Clefts of the Lip and Palate

Evidence based

Clinical Practise Guideline

Developed on initiative of the Netherlands Society of Plastic Surgery by the Knowledge Institute of the Dutch Federation of Medical Specialists.

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This Evidence Based Guideline for Clefts of the Lip and Palate has a modular structure.

This Evidence-Based Guideline for Clefts of the Lip and Palate follows a modular structure. Chapters or subjects are reviewed every five years as deemed necessary. The translation reflects the status after the most recent update of the Dutch Clinical Practice Guideline, completed in 2022.

The methodology employed for this guideline aligns with the detailed description provided in the Executive Summary of a prior version, which can be accessed online at: https://www.mdpi.com/2077-0383/10/21/4813

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On behalf of the **multidisciplinary working group of the Dutch Guideline**

This directive was drawn up at the initiative of the Dutch Association for Plastic Surgery

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Clefts of the Lip and Palate

What is this clinical practice guideline about?

This guideline focuses on, according to current standards, the best care for children with common Clefts of the Lip and / or Palate (CLA/P) and their parents.

The guideline addresses the following issues for CLA/P:

- Genetic diagnosis Nutrition
- Lip and palate closure
- Dentistry and orthodontic treatments
- Hearing problems
- Hypernasality and nasal correction
- Bone in ghatho procedure (closure of jaw gap and palate) Psychosocial
- counseling
- Organization of care
- Information to parents and policies for referral in case of suspicion of prenatal CLA/P
- Confidence of diagnosis in prenatal detection of CLA/P by ultrasound.
- Treatment team requirements for prenatal counseling
- Potential for additional birth defects in prenatal examinations when a CLA/P has been identified and the possibilities of further prenatal genetic testing have been identified.
- Counseling in prenatally established CLA/P in a prenatal diagnostic center medical topics durprenatal
- counseling in diagnosis of CLA/P
- Pregnancy termination in diagnosis of CLA/P
- Location for delivery in the case of prenatally established CLA/P
- Practical matters concerning the birth of a child with CLA/P, such as nutrition etc.
- Requirements for feedback about the birth in prenatally established CLA/P.
- Possible reduction of the risk of CLA/P by administering additional folic acid around fertilization and in the first weeks of pregnancy.

Who is this guideline meant for?

This guideline is intended for all caregivers involved in the care of patients with a CLA/P and in the prenatal care and counseling of parents who are expecting a child with a CLA/P, with or without additional birth defects.

For patients

‘Schisis’ is the Dutch word for congenital clefts of the lip, alveolus (jaw) and / or palate. The cleft may be limited to the upper lip but may also extend further into the upper jaw and palate or into the nose. Sometimes there is only a gap in the palate. In that case, nothing can be seen on the face. A cleft of the lip can be detected by ultrasound prior to birth (i.e., prenatal), isolated clefts of the palate are however difficult to see on ultrasound prior to birth.

How was the guideline formulated?

The initiative for this guideline comes from the Dutch Association for Plastic Surgery (NVPC). The guideline was drawn up by a multidisciplinary committee with representatives from general practitioners, midwives, gynecologists, pediatricians, ENT specialist (otorhinolaryngologists), plastic surgeons, maxillo-facial surgeons , orthodontists, (pediatric) dentists, speech and language therapists, clinical geneticists, specialized nurses, medical psychologists, Ortho pedagogues and social workers. During the development of the guideline, there was a specific focus on identifying the patient perspective. A representative of the patients' association CLA/P Nederland took part in the working group.

Genetic diagnosis in Clefts of the Lip and Palate

Primary question

What is the result of various genetic tests in patients with an isolated cleft of the lip, alveolus and/or palate?

Recommendation

Recommendation for the physician/professional who establishes CLA/P
Discuss the following with each CLA/P patient and/or parents of each CLA/P patient (born/unborn):

- that genetic factors can play a role in CLA/P
- the possibility of a reference to a clinical geneticist (preferably linked to a CLA/P team) to discuss the possibilities of:
    1. genetic diagnosis
    2. possibility of a repeat
    3. prenatal diagnosis

In a postnatally established CLA/P, accelerate the referral to a clinical geneticist if there are additional problems such as growth and nutrition problems, associated abnormalities, developmental retardation, specific suspicion of syndromic diagnosis and/or chromosomal aberration.

Recommendation for the clinical geneticist/medical specialist
Cover the following topics during genetic counselling with the patient/parents:

- History and family history focused on CLA/P
- Perform a physical and dysmorphological examination and clinical photographs on an established CLA/P
- Discuss the option of genetic diagnostics
- Discuss that the result of genetic diagnosis may depend on type of CLA/P and other ancillary congenital abnormalities and onerous family history
- Discuss the possibilities of any unclear results or side-effects.
- Discuss the possibility of storing umbilical cord blood DNA or blood collection during surgery that can be used for future DNA testing.

Aim for personalized genetic diagnostics and consider when choosing a particular genetic test:

- type of CLA/P
- presence of additional symptoms
- family history.

For assistance in choosing the genetic test, refer to “Recommendation for optimal strategy for genetic diagnosis in CLA/P and organization of genetic diagnosis".

Refer patients and/or parents to websites/other resources on genetic diagnostics/unclear and side-by-side findings.

Refer patients and/or parents to health care professionals or CLA/P Nederland for information on diagnosis, psychosocial guidance and contact details of fellow-patients.

Recommendation for optimal strategy for genetic diagnosis in CLA/P and organization of genetic diagnosis
When selecting a particular genetic test, consider the type of CLA/P, the presence of additional symptoms and family history. Use the strategy below when choosing a genetic test.

Isolated CLA:

1. Consider CLA/P gene panel analysis in trio (incl. CVN Analysis)

Isolated CLA/P and CP:

1. CLA/P gene panel analysis (incl. CNV analysis) in trio
2. Consider supplementing with SNP array and/or other gene panels

Isolated S with a responsible family history

1. CLA/P gene panel analysis (incl. CNV Analysis)
2. Consider expanding with SNP array and/or other gene panels – possibly followed by open exome analysis.

CL, CL/P or S with associated aberrations and/or suspected chromosomal aberration

1. SNP array
2. CLA/P gene panel analysis in trio, if necessary, in addition to other gene panels, with subsequent open exome analysis, if strong suspicion/VUSSES supplemented with RNA analysis/whole genome sequencing/testing other tissue etc.

Organization of genetic diagnostics
Consult with clinical geneticist and laboratory specialist involved about (re)classification of found genetic variants of unclear clinical significance (in a multidisciplinary context).

Notify the laboratory specialist about:

- the conclusion of the (syndrome) diagnosis
- adjustment of the VUS classification based on clinical, or segregation studies performed within the family.

Within the laboratory, consider an annual evaluation of the results of the genetic studies carried out to gain insight into the results of the diagnosis performed.

Form a national multidisciplinary CLA/P work group (from VKGN, VKGL, NVSCA) and organize a consultation between the different centers of expertise so that complex genetic results can be discussed.

Consider establishing a nationwide database to determine genotype phenotype correlations that will contribute to the interpretation of VUS-s.

Considerations

Advantages and disadvantages of diagnostic tests

Despite no studies were found in which the yield of different diagnostic tests in isolated clefts of the lip and/or palate has been compared, studies do provide information about the different diagnostic genetic tests.

In general, the diagnostic tests could be divided into two types; array-based methods (identifying minor chromosomal anomalies; microdeletions and microduplications) and sequencing methods (identifying gene variants).

Copy number variant analyzes (invasive genetic testing)

Large structural alterations of the genome and deletions and duplications of genomic regions termed copy number variations (CNVs), have been studied in patients using classical genetic analyzes such as FISH, array CGH or, more recently, SNP arrays (CONTE, 2016). Also, some studies mention karyotyping, identifying numerical and large chromosomal anomalies. However, small microdeletions and - duplications will be missed by conventional karyotyping.

Purple (2012) conducted a systematic review to provide a basis for prenatal invasive diagnostics by investigating the prenatal and postnatal prevalence of associated anomalies and chromosomal defects related to . They provided a systematic search and used data from the Dutch Oral Cleft Registry to investigate the prevalence of associated anomalies and chromosomal defects both prenatal and postnatal. This review also provided recommendations for diagnostic genetic testing for different types of . This review included 20 studies: 3 prenatal, 13 postnatal and 4 combined. This review concluded that array CGH should be considered in case of isolated oral cleft lip on prenatal ultrasound, because the absence of associated anomalies does not exclude the possibility of the presence of an underlying chromosomal defect. The chance of finding chromosomal deficits seems to depend on the type of . For example, in

presumed isolated CLAP or CP array-based methods are recommended. However, it should be considered that genetic techniques included in the review of Maarse (2012) are nowadays at least (partially) replaced by newer diagnostic genetics tests.

The study of Szczaluba (2015) assessed the utility of array comparative genomic hybridization in 53 Polish newborns with presumed isolated . Szczaluba identified 8 unique CNVs in a total of 8/52 patients (15%) using array CGH, including 3 deletions and 5 duplications. The largest rearrangement could be confirmed by karyotyping.

The study of Cao (2016) highly recommends chromosomal microarray analysis (CMA) in prenatal invasive genetic testing, not only for syndromic oral cleft cases but also for non-syndromic cases with soft markers in ultrasound (such as a single umbilical artery). CMA is a variant of array CGH/ SNP array method. The CMA analysis showed an improved detection rate of 15.3% for pathogenic copy-number variants compared with 10.5% for conventional chromosome analysis. Candidate genes including *CRKL, AKAP8, SYDE1, BRD4* are worthy of further investigation regarding their role in human palatogenesis.

In the study of CONTE (2016) 45 potential candidate genes for deletions and 27 for duplications were found, including several known causative genes for , such as *SATB2* and *MEIS2*, and genes that are associated with or development of . This study found 34 deletions and 24 duplications in genes that have not previously been associated with .

In conclusion, the above discussed studies demonstrate genetic testing (including karyotyping, FISH, array CGH, and SNP array) can reveal structural and numerical chromosomal anomalies and CNVs in cases. However, the studied population and the genetic techniques differed between the different studies. Even, the resolution of the SNP array analyses can differ between laboratories. Therefore, the outcome of these studies cannot be compared.

Next-generation sequencing methods

Next-generation sequencing methods like whole exome sequencing (WES) in family-based designs offer important advantages for identifying gene variants causing complex and heterogeneous disorders like (Bureau, 2014, Basha, 2018).

Bureau (2014) conducted a study with WES to search for variants causing using affected relatives from 55 multiplex families. Rare single nucleotide variants (SNVs), detected with WES, shared by affected relatives in 348 recognized candidate genes were examined. These 348 candidate genes consisted of 334 autosomal candidate genes for oral clefts (Jugessur, 2009) plus 14 recently confirmed genes and regions yielding genome-wide significance in a meta-analysis (Ludwig, 2012) and a replication study (Beaty, 2013). Bureau (2014) found five novel and potentially damaging SNVs shared by affected distant relatives (*CDH1, FGF8, FGFR4, TRPS1, FTCD*). One damaging SNV in *CDH1* was shared by three affected second cousins from a single family, indicating that this SNV is very unlikely to occur by chance alone.

The study of Basha (2018) also reports on gene variants causing syndromic CL/P using WES. They tested a cohort of 84 individuals diagnosed with non-syndromic CL/P from multiplex families (n=46) to find rare

Variants in genes causing syndromic CL/P. Patients included in this study had a normal karyotype, the majority had been tested for a 22q11.2 deletion and an*IRF6* mutation (van der Woude syndrome). Patients were diagnosed with bilateral CL/P (n=7), unilateral CL/P (n=16), unilateral cleft lip (CL)(n=8), cleft palate (CP) (n=33), CP posterior (n=7), submucous cleft palate (SMCP)(n=2), SMCP with bifid uvula (n=2) and velopharyngeal insufficiency (n=9). Genetic variants were analyzed independently in each family and each subject. The following four mutations were found in four different genes in five patients: *TP63* (1 family), *TXC1* (one family), *LRP6* (one family) and *GRHL3* (two families). The four mutations co-segregated with the oral cleft in an autosomal dominant manner in all families. This study shows that patients diagnosed with isolated CL/P still can carry a mutated gene causing the CL/P, whole-exome sequencing (WES) / next generation sequencing is therefore recommended when there is a family history with CL/P (Basha, 2018). In 10% of the patients with non-syndromic CL/P with a positive family history a causative mendelian mutation could be identified. It could be that in an important percentage of the remaining cases, the same genes are involved due to an indel or copy number alteration (CNVs) not easily detectable by WES. Whole genome sequencing will therefore likely be the best choice for diagnostic screens of families with a history of non-syndromic CL/P (Basha, 2018).

WES is increasingly used in the Netherlands in both isolated as syndromic . In the Netherlands, however different strategies are used in the cleft centers around the country. At first, a cleft gene panel analysis can be done. When multiple congenital anomalies are present, analyzes of all OMIM morbid genes (based on WES) or a complete trio WES with analyzes of the total exome (open exome) can be performed. In trio WES analyzes DNA of the parents is included. These tests are offered in a postnatal, but also in a prenatal setting. Gene panels do have differences regarding content, filtering (single versus trio analysis) and classification of variants can differ among centers.

Recently, a retrospective study was performed to obtain insight in the diagnostic yield of cleft gene panel analyzes in UMCU (unpublished data). The yield of the gene panel analysis was evaluated from 2015-2020. In this period the gene panel was updated, and the number of genes included in the gene panel is expanded (156 to 195 cleft related genes) (https://www.umcutrecht.nl/nl/next-generation-sequencing-ngs).

In this study 212 patients were included. Most genetic tests were done for CP (103, 48.6%), followed by (77, 36.3%) and CL (25, 11.8%). In 7 cases (3.3%) cleft type was not defined. All cases underwent cleft gene panel analyzes and, in some cases, additional genetic testing (for example ID gene panel, mendeliome or trio WES) was performed.

Cleft gene panel analyzes revealed a genetic (syndromic) diagnosis, by identification of a pathogenic variant (P) and clinical confirmation of the diagnosis in 11.3 % (24/212) of the cases. Classification of a gene variant of unknown significance (VUS) often required integrated analyzes of genetic and clinical data (including pedigree) and regularly subsequent segregation analyzes in the family had to be performed.
In (3.8 % (8/212) a causative genetic diagnosis was confirmed by additional genetic testing. Most genetic diagnoses could be confirmed in CP cases (50%, n=16); versus CL(A)+P) (40.6%, n=11) and CL (9.4%, n=3). In one case the cleft type was not defined.

We realize this retrospective inventory probably reflects the outcome of a biased population, because in general practice genetic testing is probably more often performed in children with additional minor or major anomalies or congenital abnormalities and in cases with a positive family history for clefting.

In addition to gene panel analyzes and WES, genome wide methylation tests (Episign ©) can be offered to confirm a suspected diagnosis, associated with a specific methylation profile (Aref-Eshghi, 2019; 2020).

Summary
In conclusion, previous studies and the inventory of a Dutch cleft population (n=212) demonstrated broad genetic testing can reveal underlying genetic diagnosis in syndromic clefting but also in cases with (apparent) nonsyndromic isolated clefting. Additional anomalies and family history of clefting might indicate an underlying genetic cause of the cleft. The genetic diagnoses are most frequently identified in cases with CP and .

Unfortunately, the current literature does not provide information about the exact yield of different diagnostic genetic tests in an unbiased well subphenotyped cleft population. More specific, the type of clefting in these studies are not uniformly subclassified according to the subclassification proposed by Dixon (2011), Mc Bride (2016), Pool (2021) and Vermeij-Keers (2018). Furthermore, the genetic techniques differed between the various available studies.

Further studies, including broad genotype-phenotype evaluation in well subphenotyped population and treatment outcome studies, are necessary to define those children in which genetic testing will have most benefit and determine the optimal strategy of genetic testing in cleft cases.
On the other hand, literature and the retrospective study conducted by UMCU showed that (complex) genetic testing can prevent a long Diagnostic Odyssey. Furthermore, identification of genetic anomalies will allow tailored medical care.

<u>Values and preferences of patients and their parents or guardians</u>
While genetic testing can reveal a genetic cause of requiring specific medical care, the advice is to refer all patients with (pre- and postnatally), with consent of patient and/or parents, to a department of genetics for genetic counseling. So, they can be informed about the genetic aspects of , genetic testing, their recurrence risk, and prenatal diagnostics.

It is of great importance that genetic testing is based on shared decision making and personalized medicine, where clinicians (clinical geneticist, gynecologist, and/or plastic surgeon) and patients work together to make individual decisions about invasive prenatal diagnostics and the choice of the genetic test. In this process the outcome is based on clinical evidence and expected outcomes with inclusion of patients and/or parents' preferences and values.

Parents of children with and patients with should be informed about all options of genetic testing with the pro and cons, including information on incidental findings, and the possibilities of advanced ultrasound research. After consultation it remains to the parents to decide about (further) diagnostic testing.

Professionals should realize that some parents and/or patients do not prefer invasive prenatal testing when a is observed in an unborn child and individual considerations of pregnant couples can differ enormously. Also, religion can play a significant role in the decision-making process. However, referral of parents with a fetus with to a clinical geneticist is important to discuss the options for further clinical genetic testing and outcomes of these tests.

Guidance of parents in this process is of great importance. Moreover, some parents might be confronted with a severe (lethal) disorder in their child and must decide on continuation or termination of pregnancy (TOP).
However, it is also possible that a clinical genetic diagnosis helps in deciding for optimal peri- and postnatal care.

Parents of a child with and patients with , should also be informed about their recurrence risk and options for future pregnancies, e.g. preimplantation genetic testing (PGD). Furthermore, it is important that parents and future parents are aware of their right to get a second opinion and they can contact patients organizations for more information and empowerment, for example in the Netherlands: www.CLA/Pnederland.nl, http://www.erfelijkheid.nl/(date: May 2021).

Costs/Finances

With clinical application of whole-exome and whole-genome sequencing in cases a diagnosis can be made in an early stage, preventing a Diagnostic Odyssey. Also initially in presumed isolated clefts.

The Dutch Health Council indicates that early diagnosis is extremely important. Knowing the genetic origin will lead to better treatment and timely interference for possible future symptoms related to their genetic disorder. Moreover, early diagnosis prevents unnecessary second opinions and additional diagnostic tests and can thus limit the negative consequences for the well-being of the child and the parents. Futher, parents can be informed about risks of recurrence.

The Dutch Health Council states that early genetic testing should be used instead of introducing heel prick screening for untreatable conditions.

On the other hand, an early diagnosis can also be stressful for the parents, while it may take a long time for symptoms to arise. Also, the clinical spectrum of certain diagnoses can be broad, which can create uncertainty.

DNA testing in the Netherlands is totally reimbursed by the basic insurance, however, the mandatory excess will be paid first. It is important that patients are informed about reimbursement rules.

The actual cost-effectiveness of genetic testing cannot be determined until the yield of genetic testing has been determined in an unbiased population, and follow-up studies have been performed to analysis the effect of a specific diagnosis, considering the quality of life of people with and their parents.

Acceptance, feasibility and implementation

Nowadays, genetic counselling and testing is increasingly offered to (future) parents of a child with in

both prenatal and postnatal settings. We have inquired at our eight genetic Centers which policy they currently used. The outcome demonstrated all Centers, despite variations in genetic strategy, discussed and offered genetic testing.
The clinical geneticist is not always present during consultation at the prenatal or postnatal cleft team. When (future) parents opt for genetic testing, they are referred to the genetics department and receive an invitation for a separate consultation. Depending on personal, cultural, and familial considerations and possible consequences, parents can decide which genetic testing will be performed. This decision should be made on accurate information, therefore shared decision making, and counselling is essential, and even more important than diagnostic outcome.

Rational

1. Recommendation to the physician/professional who determines CLA/P

The review of Maars (2012) and the inventory of the outcome of genetic analyzes in a Dutch cleft population (unpublished data) demonstrates genetic testing can identify (extreme) rare genetic disorders. Confirmation of a genetic diagnosis can optimize personalized, timely car and improve medical and genetic counselling.

In prenatally detected , advanced ultrasound (GUO) and genetic testing can lead to an underlying diagnosis.
To inform parents of a child with or patients with about the pros and cons of genetic testing and to promote personalized genetic testing, they should be offered referral to a genetic department.

2. Recommendation for the clinical geneticist/medical specialist

Most studies showed that and CP are more often associated with an underlying genetic diagnosis. The presence of additional anomalies and/or a positive family history for orofacial clefting can indicate an underlying genetic cause certain diagnoses (e.g.*CDH1, IRF6, SIX3*) are associated with variable expression and reduced penetrance.

Thus, genetic counseling should entail an extensive medical and family history, specific physical examination and dysmorphological evaluation of index and their parents (see attachment “intake form”, in Dutch).

The strategy of genetic testing in should be personalized. The type of cleft, the presence of possible additional minor and major anomalies or abnormalities and the family history must be considered in selecting the best fitting genetic test(s). Moreover, genetic testing can be different in prenatal or postnatal setting.
When a cleft is detected prenatally, DNA can be stored from umbilical cord blood for future genetic testing. After birth, blood samples can be tasks during surgery. This prevents invasive blood sampling in the child after birth.

A suggested strategy for the genetic diagnostics is discussed in "Recommendation for optimal strategy for genetic diagnosis in CLA/P and Organization of genetic diagnostics" in this module.

One should realize sequential DNA testing can be associated with increased costs and extensive DNA testing might increase the chance detecting variants of uncertain (or unknown) significance or unsolicited findings. In

Addition, an important aspect to keep in mind using next-generation sequencing technologies such as WES trio analysis, is that autosomal dominant gene variants with a reduced penetrance (e.g.*CDH1, IRF6, SIX3*) segregating in a family, might be filtered out in the data analyzes.

It is important that parents of a child with CL(A)/P and patients with CL(A)/P are informed about the different aspects of DNA testing, including yield for different cleft type, broad spectrum of cleft syndromes that might be identified, Parks can be referred to informative websites for more information (e.g. CLA/P Nederland and Erfocentrum). Parents of a child with CL(A)/P and patients with CL(A)/P should be informed about their recurrence risk and possible choices concerning future pregnancies.

3. Recommendation for optimal strategy for genetic diagnosis in CLA/P and Organization of genetic diagnosis
Genetic testing should be personalized and the type of clefting, additional anomalies and family history should be considered. The strategy, described below, should be considered.

In cases, suspected of an underlying chromosomal abnormality, SNP array is the first choice of testing. In cases, without a suspected syndrome diagnosis or chromosomal abnormality, cleft gene panel analyzes, including CNV analyzes, (WES targeting cleft related genes) should be considered as the first choice of genetic testing. By performing a trio wes, inherited variants with reduced penetrance and/or variable expression segregating in a family might be filtered out and can be missed.
In cases with associated anomalies combined SNP array and WES based cleft gene panel analyzes (including CNV analyzes) should be considered.
In cases with specific dysmorphic features and/or associated congenital anomalies and/or intellectual disability broader genetic testing (for example for ID and/ or congenital anomalies, mendeliome), specific single gene sequencing and additional trio WES) should be considered.
In case of a prenatally diagnosed , prenatal invasive diagnostics is offered (chorionic villus test / amniocentesis). Based on the presence of additional ultrasound anomalies at the moment a QF-PCR, SNP array, and/or gene panel analyzes and/or trio WES can be performed.

While prenatal genetic testing can be rather complex, for example by revealing (extremely) rare diagnoses with variable phenotypes or unsolicited findings, prenatal counselling should be performed in specialized Centre.

Strategy interpretation genetic test results:
A Dutch inventory shows that DNA testing often reveals variants of uncertain (or unknown) significance (unpublished data). While classification of a gene variant of unknown significance (VUS) requires integrated analyzes of genetic, complete phenotypic and clinical data (including pedigree), it is important VUS –es with uncertain classification are discussed by the laboratory specialist and clinical geneticist together. In addition, clinical input by other medical experts (e.g. gynecologist, plastic surgeon and pediatrician) and embryologist can be valuable to interpret a variant of unknown significance (VUS).

It is important to inform the laboratory about the eventual conclusion and genetic diagnosis of the patient after follow-up. These data are of great importance for classifying variants in future patients.

A national cleft working group bringing together a multidisciplinary panel of clinical cleft experts (including clinical geneticists, laboratory specialists, plastic surgeons, pediatricians and embryologists) from different expert Centre would promote development of specific cleft expertise. Discussing identified gene variants with uncertain pathogenicity, complex patients and novel research knowledge in a regular meeting (every quarter) would expand current knowledge.

Strategy data sharing:
Development of a biobank containing complete cleft data of the Dutch population, including genetic and phenotypic data, will help to identify phenotype genotype correlations and determine pathogenicity of variants of unknown significance (VUS-ses).
It would be desirable to have a national database containing both phenotypic (subclassification) and genetic data (including pathogenic variants as well as variants of unclear significance (VUS)) or patients in the Netherlands. The possibility to connect to current national databases of the NVSCA and ICHOM – International Consortium for Health Outcome Measurement) could be explored.

Although, privacy issues and government rules might be limiting factors in implementation of such a database.

Innovation gene panel analysis:
It is also noted that increasing knowledge urge a regular update of the gene panels. Certain genetic causes of clefting can be missed because novel cleft genes are not yet included in the gene panel.

Cost-effectiveness:
For now, the actual benefit and cost-effectiveness of genetic testing cannot be determined until the yield of genetic testing has been investigated in an unbiased population, and follow-up studies have been performed to analysis the effect of a specific diagnosis, considering the quality of life of people with and their parents.

Background of the Substantiation

With the advance of prenatal ultrasound screening genetic testing for has shifted more and more from postnatal to prenatal testing and counseling. At the same time technologic developments have diminished the differences between genetic tests available prenatally and post postnatally. So tasks from a genetic testing point of view the differences between prenatal and postnatal testing are vanishing. Therefore, the working group decided to keep all the information in one module instead of splitting in pre- and postnatal testing. In the literature review, rationale and recommendations about genetic testing the results are applicable in the prenatal and postnatal setting unless specified otherwise.

A cleft of the lip, alveolus and/or palate (S) is a congenital abnormality with a complex etiology and a.

broad spectrum of causes consisting of - among other factors - chromosomal abnormalities, several gene mutations, teratogens, nutritional deficiencies and infections during pregnancy (Dixon, 2011; Leslie, 2013; Conte, 2016).

is often an isolated condition but can be associated with multiple congenital anomalies, development delay and/or be part of a syndromic diagnosis. More than 275 syndromes have been described in which is a characteristic symptom (Setó-Salvia, 2014). Depending on the underlying cause, monitoring for specific features might be required. (Maars, 2012; Setó-Salvia, 2014).

Therefore, recognition of a syndromic/genetic cause for the cleft is important for tailored and personalized care and long-term management, but also crucial for accurate genetic counselling. The recurrence risk for non-syndromic and syndromic cleft can differ considerably.

However, it might be difficult to distinguish syndromic and non-syndromic S. Prenatally, certain syndromic features (e.g. lippits in Van der Woude syndrome) can not be detected by ultrasound. After birth, minor syndromic features can also be hard to recognize (e.g. distichiasis in Lymphedema-distichiasis syndrome), OR only appear at a later stage (e.g. myopia in Stickler syndrome, Lymphedema-distichiasis syndrome (Rozendaal, 2012, Setó-Salvia, 2014). Furthermore, cleft syndromes can be associated with reduced penetrance.

Rittler (2011) reported that 7 to 9 % of the children with that are initially thought to be isolated cases are found to have associated abnormalities. Furthermore, various known 'syndromic' genes can also be responsible for non-syndromic , demonstrating isolated and syndromic clefting can be part of an overarching spectrum (Jezewski, 2003; Leoyklang, 2006; Leslie, 2015a and b, Moreno, 2009; Rahimov, 2012, Setó-Salvia, 2014, Brito, 2015).

In 2021, there are various options available for genetic testing to obtain a diagnosis, including targeted gene testing, gene panel analysis, Whole Exome (and Genome) Sequencing and CNV analysis and in specific cases methylation assays and RNA analysis.

However, the optimum strategy for genetic testing, considering the yield of genetic testing, clinical impact, effect on treatment outcomes and benefit for patients and parents, still must be determined.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of different genetic tests in isolated clefts of the lip and/or palate on the diagnostic yield in isolated clefts of the lip and/or palate?

P: Patients with isolated cleft lip, alveolus, and/or palate or pregnant women undergoing additional testing for suspected cleft lip, alveolus, and/or palate in their child;
I: diagnostic genetic tests (copy number variant (CNV) analysis (e.g. array comparative genomic hybridization (CGH), SNP array, CMA), next generation sequencing, e.g. gene panels, whole exome sequencing);
C: Comparison of the tests above;

R: long term follow-up of children with apparently isolated cleft to identify late onset features an underlying genetic/ syndrome diagnosis;
O: yield, sensitivity, specificity, diagnostic accuracy.

Relevant outcome measures
The working group considered yield as a critical outcome measure for decision making. The yield of a diagnostic test is defined as the ability to identify underlying genetic variants as cause of . Sensitivity, specificity, and diagnostic accurateness were considered as important outcome measures for decision making. The working group considered a sensitivity or specificity above 80% as sufficient.

Search and select (Methods)
The previous module on genetic testing in the 2018 edition of the guideline was based on expert opinion and did not provide a systematic search. The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 13th of February 2020. The detailed search strategy is depicted under the Tab Methods. The systematic literature search resulted in 165 hits. Studies were selected based on the following criteria: patient population consisting of children (< 18 years) with (both syndromic and non-syndromic) and first-degree relatives (parents or siblings), or pregnant women of a child with possible S. The intervention was a diagnostic genetic test: copy number variant (CNV) analysis (for example array comparative genomic hybridization (CGH), SNP array, CMA), next generation sequencing, e.g. gene panels, whole exome sequencing). Eight studies were initially selected based on title and abstract screening. After reading the full text, these eight studies were excluded since they did not compare diagnostic Tests (see the table with reasons for exclusion under the tab Methods). Thus, no studies were selected for the literature summary.

Results
No studies were found that compared the yield and benefit of the genetic test and provided insight into the total yield, sensitivity, specificity, and diagnostic accurateness of these different tests.

Reporting

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For full reports, evidence tables and any related products, please refer to the Dutch Guideline on-line Database:

https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html

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Feeding in patients with a CLA/P

This module is divided into the following sub-modules:

- Feeding after birth in patients with a CLA/P
- Postoperative feeding in patients with a CLA/P

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

Feeding after birth

Primary question

What is the best way to feed a newborn baby with a cleft palate (with or without a cleft lip / alveolus)?

Recommendation

Preferably start oral feeding post-natally. Tube feeding as a primary feeding is not recommended.

In consultation with parents, choose an appropriate individualized and comfortable method of feeding a baby with a cheilo, cheilognatho and/or palatoCLA/P. Consider the following factors: breastfeeding versus bottle feeding, different types of bottles and (dummy) teats, feeding posture.

In the case of a palatoCLA/P, use a modified bottle postnatally, such as a ‘squeezable bottle’ or ‘feeder-driven bottle’ (Medela Special Needs Feeder) or an ‘infant-driven feeding system’ (Dr Brown's Specialty Feeding System).

In the case of a palatoCLA/P, consider the Nuby Natural Touch bottle for the milk thickening.

Easily turn to the CLA/P team logopedist (or neonatology unit) for problems such as insufficient intake, prolonged feeding time (> 30 minutes at a time) or pressure spots on the palate/nasal septum.

From the age of 4 months onwards, spoon feeding may be started as an alternative route of administration in addition to breast/bottle feeding.

Take a multidisciplinary approach to feeding a baby with a palatoCLA/P in order to achieve normal growth for the child.

Considerations

<u>Advantages and disadvantages of the feeding methods, and quality of the evidence</u>
One recent systematic review was found that described the effect of feeding interventions on growth and development of infants with cleft lip and/or palate. Unfortunately, only two RCT studies were included in this review that answered our clinical question and provided a limited level of evidence, due to conflicting results and small study sizes. The overall level of evidence was very low. Based on the literature it is uncertain what the effect of different feeding techniques is on patients' growth. Furthermore no conclusions could be drawn on patients' nutritional intake and their parents' quality of life.

Two studies compared the use of a standard bottle and pacifier to the use of the Special Needs Feeder (squeezable). Both studies used weight, height and head circumference as outcome measures. No significant differences were found in these outcome measurements at different time points during the study. The aspect

“Quality of life” was experienced as better in the group with the Special Needs Feeder. However, this was not significant. Adjustments to the Special Needs Feeder were required less often than to the standard bottle (Shaw, 1999; Brine, 1994).

In two studies (Prahl, 2005; Gorstein, 1994) the possible contribution of wearing an feeding plate until the soft palate was closed, was investigated. The outcome measures were weight in relation to height, height in relation to age, and weight in relation to age (Z-score). There was no significant difference found in any of the studies. However, in Prahl's study (Prahl, 2005) a significant difference was reported for children with a complete cleft- lip-palate as compared to the normal values for Dutch children without cleft lip and palate.
The children with a cleft were lighter and shorter in the first year of life as compared to non-affected Dutch children. Whether or not an feeding plate was worn, did not matter. This measured difference disappeared in the following years.

In the systematic review (Penny, 2021), two studies evaluated the possible added value of feeding plates. Although no statistical significant differences were found, the use of an feeding plate in conjunction with other interventions (i.e. specialty bottles, lactation education), seem to have added value (Goyal, 2014; Reid, 2004). A possible disadvantage of using an feeding plate is, however, the fact that it has to be manufactured (cost aspect) and regularly adjusted due to the growth of the child, which can cause stress for the baby and its parents. It requires frequent visits and can lead to problems such as fungal growth on the palate due to poor oral hygiene (Goyal, 2014).

When feeding a child with a cleft palate and an exposed vomer a pressure sore can develop on the vomer (due to repeated local pressure from the nipple of the bottle). This sore spot can certainly have a negative impact on the effectiveness of the baby's drinking behavior and the general wellbeing because of the pain this gives. Regular checks of the possible occurrence of such a pressure spot as well as an explanation to parents that changing the teat position is important to prevent this are therefore very important in these first weeks after birth.

Squeezable bottles may be more user-friendly for the parents, although current evidence does not suggest that there is a difference in squeezable and rigid bottles, regarding to normal growth (Penny, 2021).

In conclusion, few good studies were carried out to find the best way of feeding babies with cleft lip and palate and the available evidence has a low scientific level. It is not yet clear how the normal sucking- and swallowing skills develop in children with cleft lip and palate compared to the sucking- and swallowing skills in babies without cleft lip and palate (Palmer, 1993). Interventions are merely based on expert opinions, rather than on scientific evidence. Babies with cleft lip and palate are usually excluded from conducted studies about sucking skills. Palmer's studies generally assume that the sucking skills in babies with cleft lip and palate is fundamentally different, but there is no evidence for this.

More physiological functional research is needed to gain insight into the sucking- and swallowing skills of babies and children with a cleft of the palate (with or without cleft lip/alveolus). Research is also needed to provide evidence about the incidence of feeding problems with risk factors such as postoperative recovery compared to that of healthy children. The results of these studies should clarify whether and, if so, what the

differences are in sucking- and swallowing skills in healthy babies and children compared to babies and children with a cleft of the palate (with or without cleft lip/alveolus). Further research is also needed, both postnatal and postoperatively, into the way in which children with a cleft lip are able to compensate for the anatomical abnormalities in the swallowing process. Additional evidence is also needed on the long-term effects of abnormal sucking- and swallowing skills on further development of the process of swallowing.

Values and preferences of patients and their parents or guardians

In the context of intraoral sensorimotor development, it is important to normalize the sucking skills, swallowing pattern and the eating pattern later on, as quickly as possible by adopting a natural diet. If tube feeding is necessary, this should be done as short as possible. Children receiving tube feeding are often more sensible around the oral cavity. Combining tube feeding with oral feeding reduces the sensibility and facilitates, for example, acceptance of teeth-brushing later on. Preferably tube feeding should be given in combination with oral nutrition or oral stimulation.

For children with a cleft lip, grasping the breast/pacifier can be difficult. This makes it more difficult for them to suck the milk out of it. In infants with a cleft of the lip (with or without the alveolus) only, breastfeeding can still be feasible. A lactation consultant can provide the parents with valuable guidance regarding different options including breastfeeding positions.

In case of a cleft palate (whether or not in combination with a cleft lip or cleft alveolus), the child is not able to suck sufficiently with normal effort. Because of the open communication between mouth and nose, no vacuum can be created. Breast feeding and the use of a regular bottle will not lead to sufficient nutrition due to the limited suction skills.

In addition, children with a cleft palate have a high risk of nasal regurgitation during feeding. A special needs feeder such as the Special Needs Feeder (Haberman) from Medela (plastic bottle with valve and special teat) will be of great help. By squeezing the teat while sucking and using the 1-2-3 system, the child's suction skills can be supported.

Mildly to moderately thick fluids (IDDSI 2-3) cannot be used in combination with the Special Needs Feeder. The Nuby (Natural Touch Softflex) teat can be used in children with reflux complaints who are prescribed thickened milk.

The Nifty cup, Paladai and spoon feeding can sometimes be used as alternative methods to breastfeeding (McKinney, 2020 and Duarte, 2016) but no convincing evidence to support this has been found in the current literature.

For children with a cleft lip and palate and their parents, it is very important that they are very well guided in the feeding process directly after birth. In case of nutritional problems, the speech and language therapist of the cleft- or neonatal team should be called for help. This speech and language therapist has knowledge of and experience with normal drinking and eating development and abnormal feeding induced by a cleft palate (with or without Cleftlip/alveolus). Furthermore, the speech therapist must be aware of the different ways of feeding and the use of the different materials and feeding positions. Indicators of quality for the feeding

process are: growth (length and body weight), aerophagia, dysphagia, nasal regurgitation, flow, and feeding time. The confidence of parents and caretakers in good guidance and the well-being of the child and the quality of the feeding session are priorities. If there are no specific problems, another healthcare professional can take over delegated tasks from the speech and language therapist In addition to a speech and language therapist, a psychologist or a social worker could provide valuable guidance for parents in case confidence of the parents remains an issue. More information on psychosocial guidance is provided in chapter 10.

Educational programs for parents aim to improve their knowledge about cleft conditions and appropriate feeding strategies. These programs represent a promising and cost-effective intervention as they have shown to facilitate infants growth (Penny, 2021).

We expect that with the implementation of PROMS in relation to feeding, in the near future, we can have a better insight in the feeding patterns of cleft children. These PROMS may also help parents to communicate in a structured way about the feeding problems of their cleft children. This in turn can help us as cleft care professionals to get a better understanding of the feeding difficulties in cleft children.

In conclusion, it can be stated that there is no clear preference for one way of feeding or the other; this depends on the child, the parents and the type of cleft lip and palate (Goyal, 2014). Important principles are:

- Ensure that a speech therapist is present for each cleft- or neonatal team, with knowledge of and experience with normal drinking and eating development and the effect of cleft lip and palate on this. The speech and language therapist of the cleft team must participate in the NVSCA speech therapy working group (see chapter on organization of care);
- Tailored care must be given around the nutrition of a child with a cleft lip and palate. Every parent and every child needs a different advice. The speech therapist must know and be able to apply the existing Special Needs Feeders;
- During pregnancy (after the 20-week ultrasound) and/or after birth, the cleft team provides information about the cleft lip care path. This includes information about the possibilities and impossibilities of breast and bottle feeding by the speech therapist or by a member of the cleft team from another discipline in accordance with the prescriptions of the speech therapist.

Costs/Finances

The costs of a speech therapist and the special needs feeder seem to be no problem in the Dutch setting. Also these cost do not outweigh the costs in case of a hospital admission of a cleft child with feeding problems.

Acceptance, feasibility and implementation

For children with a cleft lip and palate, adequate nutritional supervision is necessary, so the child will be fed appropriately and an adequate oral intake is maintained. Pandya and Boorman (2001) describe a significant decrease in failure to thrive in children with cleft lip and/or palate with adequate and intensive supervision. It is important that the child is in a good nutritional state to build up resistance to infections. This is also important to be able to survive the operative phases well (Reid, 2004; Hughes, 2013).

Feeding a child with cleft lip and palate can be frustrating and stressful for the parents. When these moments of togetherness are disturbed by crying and/or restlessness in the baby, it can make the parents insecure with the risk of disturbed or less good bonding. That is why good adequate guidance is important (Miller, 2011).

Background of the Substantiation

Feeding is a primary life need from birth. In children with cleft palate (with or without a cleft lip / alveolus), feeding can cause problems. The growth and weight gain of the baby and the bonding with parents can be disturbed as a result. Guidance by a nurse specialist and/ or a (pre-verbal) speech therapist from the cleft- team is therefore important.

Newborns use reflexes to suck, swallow and breathe during the first few weeks. An efficient sucking motion is achieved by creating negative intra-oral pressure with good nipple/teat enclosure and soft palate elevation (Reid, 2004). This is done by a rhythmical movement of tongue and lower jaw, closing the nasopharynx and increasing the intra-oral space. A positive pressure is thereby applied to the nipple/teat with the lips, facilitating milk transfer out of the nipple/teat. Together with the suction, this makes efficient feeding possible.

In babies born with a lip alveolus cleft only (with an intact palate), drinking from the breast or bottle usually proceeds with little or no problems. If necessary, a small adjustment in position, teat, or support of the base of the mouth and lips will usually suffice.

Babies born with a cleft palate only, or a congenitally short palate, are at risk for developing feeding problems. This also applies to babies with a cleft lip, alveolus and palate. When a cleft palate exists, the baby is generally unable to close off the oral cavity from the nasal cavity. As a result, the baby cannot effectively create a sufficient vacuum during sucking. The vacuum stabilizes the nipple or teat and is necessary to actively obtain (breast) milk from the breast/teat (Watson, 2001; Sell, 2001; Grunwell, 2001).

Research shows that a less efficient sucking pattern is present in children with nonsyndromic unilateral complete cleft lip, alveolus and/or palate (compared to peers without cleft) (Maserati, 2007; Besell, 2011). This can lead to longer feeding time, and increased fatigue. Furthermore, it appears that these infants with a cleft require proportionally more energy, to ingest a relatively small amount of milk than their healthy peers (Sprinted, 1995; Bardach, 1995).

The main goal of nutrition in newborns is normal weight gain and length growth. In this chapter, we try to provide the most appropriate forms of administration of nutrition (milk) in newborns with cleft palate (with or without a cleft lip / alveolus). To monitor feeding, the following quality parameters can be tasks into account: Growth and length of the child, aerophagia, dysphagia, nasal regurgitation, flow, feeding time and parental confidence. The well-being of the child and the quality of the feeding session for a child and its parents is paramount. The various special needs bottles: squeezable bottles or feeder-driven bottles

(Medela Special Needs Feeder) and 'infant-driven feeding systems' (Dr. Brown's Specialty Feeding System) and alternative feeding systems such as syringe, cup feeding and spoonfeeding will be examined for this chapter. The use of feeding plates and educational programs for parents will also be evaluated.

Conclusions

1. Amount of feeding intake (crucial)

- GRADE	The level of evidence regarding the outcome measure amount of feeding intake was not assessed due to lack of studies.

2. Patient's growth (length and weight) (crucial)

Very low GRADE	The evidence is very uncertain about the effect of a rigid bottle on length and weight after 3, 6, 12 and 18 months when compared with a squeezable bottle in patients with cleft lip and/or palate. *Resources: Shaw (1999) and Brine (1994)*

3. Parents' quality of life (important)

- GRADE	The level of evidence regarding the outcome measure parents' quality of life was not assessed due to lack of studies.

Summary of literature

Description of studies

Penny (2021) describes a systematic review including RCT studies evaluating the effect of feeding interventions on growth and development of infants with cleft lip and/or palate, published between inception and May 2021. Two RCTs (n=138) included in this systematic review answered the clinical question of this chapter. Both RCTs compared squeezable with rigid bottles (Shaw, 1999; Brine, 1994). Two other RCTs studied the effect of a maxillary plate, which was beyond the scope of this chapter (Massarei, 2007; Prahl, 2005). Other RCTs in the study of Penny (2021) did not provide follow-up data on post-natal feeding for at least 12 months.

- Brine (1994) included 37 babies with cleft palate or cleft lip and palate, prior to closure. Babies in the intervention group were fed with a squeezable nurser (n=18), babies in the control group were fed with a rigid bottle with cross-cut nipple (n=13). All babies with cleft lip and palate received an intraoral maxillary obturator, regardless of treatment group. Relevant outcome measures include growth in length and weight. The follow-up was 18 months.
- Shaw (1999) included 101 babies with cleft lip (n=25), cleft palate (n=31) or cleft lip and palate (n=45). Babies in the intervention group were fed with a squeezable bottle with nuk orthodontic teat (n=49), babies in the control group were fed with a rigid bottle with nuk orthodontic teat (n=52). Relevant outcome

measures include growth in length and weight. The follow-up was 12 months.
Penny (2021) provides a narrative description of the results of each included trial and refers to the Cochrane systematic review by Bessell (2011) in which pooled analyzes of these two trials are published.

Results

1. Amount of feeding intake (crucial)

The outcome amount of feeding intake was not reported in the included studies.

Level of evidence of the literature

The level of evidence regarding the outcome measure amount of feeding intake was not assessed due to lack of studies.

2. Patient's growth (both length and weight) (crucial)

Length was described in the studies of Shaw (1999) and Brine (1994).
In the RCT of Brine (1994), data for length was provided for timepoints 6 and 18 months.
At 6 months, mean length in the rigid bottle group was 64.5 cm (SD 1.8, n=13). Mean length in the squeezable bottle group was 63.5 cm (SD: 2.5, n=18). Mean difference between the two groups was 1.00 cm (95% CI: -0.51 to 2.51), favoring the rigid bottle group.

At 18 months, mean length in the rigid bottle group was 80.6 cm (SD 2.9, n=13). Mean length in the squeezable bottle group was 81.7 cm (SD: 2.4, n=18). Mean difference between the two groups was 1.90 cm (95% CI: -0.03 to 3.83), favoring the rigid bottle group.
In the RCT of Shaw (1999), length was measured after 13 weeks, 26 weeks and 52 weeks.
At 13 weeks, mean length in the rigid bottle group was 55.3 cm (SD 2.04, n=52). Mean length in the squeezable bottle group was 55.3 cm (SD: 2.25, n=49). Mean difference between the two groups was 0.00 cm (95% CI: -0.84 to 0.84).
At 26 weeks, mean length in the rigid bottle group was 66.7 cm (SD 2.5, n=51). Mean length in the squeezable bottle group was 66.8 cm (SD: 2.18, n=49). Mean difference between the two groups was -0.10 cm (95% CI: -1.02 to 0.82), due to more length in the squeezable bottle group.
At 52 weeks, mean length in the rigid bottle group was 74.8 cm (SD 3.03, n=50). Mean length in the squeezable bottle group was 75.1 cm (SD: 2.33, n=49). Mean difference between the two groups was -0.30 cm (95% CI: -1.36 to 0.76), due to more length in the squeezable bottle group.

Weight was described in the studies of Shaw (1999) and Brine (1994).
In the RCT of Brine (1994), weight was measured after 6 and 18 months. After 6 months, mean weight in the rigid bottle group was 6.98 kg (SD: 0.76, n=13). Mean weight in the squeezable bottle group was 6.86 kg (SD: 0.36, n=18). Mean difference between the two groups was 0.12 kg (95% CI: -0.33 to 0.57), favoring the rigid bottle group.
After 18 months, mean weight in the rigid bottle group was 10.6 kg (SD: 1.1, n=13). Mean weight in the squeezable bottle group was 10.14 kg (SD: 0.7, n=18). Mean difference between the two groups was 0.46 kg (95% CI: -0.22 to 1.14), favoring the rigid bottle group.
In the RCT of Shaw (1999), weight was measured after 13 weeks, 26 weeks and 52 weeks.

At 13 weeks, mean weight in the rigid bottle group was 4.38 kg (SD: 0.51, n=52). Mean weight in the squeezable bottle group was 4.43 kg (SD: 0.51, n=49). Mean difference between the two groups was -0.05 kg (95% CI: -0.25 to 0.15), due to a higher weight in the squeezable bottle group.
At 26 weeks, mean weight in the rigid bottle group was 7.04 kg (SD: 1.56, n=51). Mean weight in the squeezable bottle group was 7.38 kg (SD: 0.73, n=49). Mean difference between the two groups was -0.34 kg (95% CI: -0.81 to 0.13), due to a higher weight in the squeezable bottle group.
At 52 weeks, mean weight in the rigid bottle group was 9.22 kg (SD: 1.22, n=50). Mean weight in the squeezable bottle group was 9.64 kg (SD: 1.06, n=49). Mean difference between the two groups was -0.42 kg (95% CI: -0.87 to 0.03), due to a higher weight in the squeezable bottle group.

Level of evidence of the literature
The level of evidence regarding the outcome measures length and weight at any timepoint started at high because it was based on randomized controlled trials, but was downgraded by three levels because of conflicting results (inconsistency, -1) and limited number of included patients (imprecision, -2). The final level is very low.

3. Parents' quality of life (important)
The outcome parents' quality of life was not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measure parents' quality of life was not assessed due to lack of studies.

Search and select

A systematic review of the literature was performed to answer the following question: What is the most efficient feeding technique for normal weight-gain in patients with cleft lip, alveolus and/or palate?
In the 2021 update of this guideline, post-operative feeding is evaluated in a separate module (module 5, postoperative nutritional care for isolated clefts of the lip alveolus and or palate).

P: Patients with cleft lip, alveolus and/or palate (postnatal) I:
1. feeding technique;
2) feeding position;
3) concsistency of nutrition (Special Needs Feeder, breastfeeding, tube feeding, spoon feeding, finger feeding, post-natal counseling, feeding-system (both bottle and nipple)).
C: other method of feeding
O: Amount of feeding intake, patient's growth (both length and weight), parents' quality of life (measured at 3, 6 and 12 months)

Relevant outcome measures
The guideline development group considered amount of feeding intake and newborn's growth (both length and weight) as critical outcome measures for decision making, and parents' quality of life as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group did not define the minimal clinically (patient) important difference for the different continuous outcome measures. Therefore, the following criteria of the minimally important difference were used for the continuous outcome measures; Standardized mean difference (SMD=0.2 (small); SMD=0.5 (moderate); SMD=0.8 (large)). No a priori criteria were set for the dichotomous outcome measures because it largely depends on its context.

Search and select (Methods)
A previous systematic search was performed for the 2018 edition of the guideline in the databases of Medline (through OVID) Embase and the Cochrane Library between 1980 and November 5th, 2014. The initial search identified 65 references of which 17 were assessed on full text.. After assessment of full text, nine studies were excluded, and eight studies were included. To update the previous search the databases Medline (Via OVID) and Embase via Embase.com were searched with relevant search terms until November 15th, 2021. The detailed search strategy is depicted under the Tab Methods. The updated systematic literature search on postnatal feeding resulted in 249 hits. Studies were selected based on the following criteria. Studies that investigated patients with cleft lip, alveolus and/or palate were selected if they compared two different feeding methods. The feeding interventions had to be studied immediately after birth. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: Amount of feeding intake, patient's growth (both length and weight), parents' quality of life. Follow-up time had to be at least 12 months.
Eleven studies were initially selected based on title and abstract screening. After reading the full text, TEN
Studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included.

Results
One study was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Post-operative feeding in patients with a CLA/P

Primary question

What post-operative feeding advice can be given to children with a CLA/P after various operations on the palate and/or jaw clevis?

Recommendation

Try to keep the way you feed as consistent as possible with the way before the operation.

Try to change the way of feeding (bottle, breast, spoon) as little as possible around CLA/P operations.

Apply the feeding recommendations as described in the summary table as far as possible.

After a bone in gnatho (BIG) procedure, advise patients not to bite the food with the front for 6 weeks.

Consider adding a bite increase if there is contact between upper and lower front for a bone in gnatho BIG procedure.

Evaluate growth and nutritional status both pre- and post-operative and consult a pediatrician if necessary.

Considerations

No studies were found that directly compared thin, fluid, soft food or tube feeding with normal/solid food until 6 weeks after palatoplasty, pharyngoplasty or bone graft procedure in children with cleft alveolus and/or palate between 6 months and 11 years old, on the outcomes: wound healing, amount of food intake/nutritional status, moving premaxilla and fistulas.

We will provide an overview of studies that indirectly assessed feeding methods and/or nutritional status in children following cleft palate or bone graft procedure.

<u>Palate repair and different feeding methods</u>
A systematic review by Duarte (2016) compared different feeding methods in children with cleft lip and palate, such as breast feeding, bottle feeding, syringe-, tube-, spoon- or paladai- feeding. For our question only studies that compared feeding methods for soft food (cup, syringe, tube or paladai) with feeding methods for solid food (spoon) in palate repair (associated or not associated with lip repair) were assessed. Bone graft procedures were not included by Duarte (2016). Studies comparing breast feeding/bottle feeding methods were not assessed.

Two studies, included and analyzed by Duarte (2016), could be assessed: Hughes (2013) compared tube feeding versus oral food intake and Trettene (2013) compared cup versus spoon feeding. Unfortunately, the studies were focused on the immediate hospital period following palate repair within 24 hours, and not the period 3 to 6 weeks post-surgery.

An overview of study characteristics, tasks from the systematic review by Duarte (2016):

Table 1 Study description Hughes (2013) and Trettene (2013) by systematic review of Duarte (2016)

Author (year)	Study design	Age range	Isolated cleft palate repair, cleft palate and lip (n, n)	Comparison	Assessed period after procedure	Assessed parameters
Hughes (2013)	Pilot study Or an RCT	5 to 10 months	32, 9	Feeding tube (n=18) vs.. Oral feeding (n=23)	Until 24 hours after procedure	Analgesia/ pain; number of painful episodes, intravenous fluids and enteral feeding.
Trettene (2013)	Prospective cross-sectional study	11 to 18 months	Not reported	Cup (n=88) versus. (n=88)	Until 24 hours after procedure; at 4 different time points	Coughing, choking, escape; accepted volume.

Tube versus oral food and cup versus spoon during the postoperative feeding period following surgical repair of cleft palate associated or not associated with lip repair
Source: Duarte (2016)

Table 2 Tube versus oral food during the 24-hour postoperative feeding period following surgical repair of cleft palate

	Nasogastric feeding (n=18)	Oral feeding (n=23)	Test statistic
Analgesia/Pain: 1) post operative morphine, mean mg/kg (range) 2) Paracetamol, mean mg/kg (SD*) 3) Ibuprofen, mean mg/kg (SD*)	1) 0.16 (0.04 to 0.31) 2) 64.4 (13.3) 3) 13.2 (8.23)	1) 0.16 (0,024 to 0.4) 2) 61.9 (14) 3) 14.6 (4.7)	1) >0.1 (Mann-Whithney test) 2) >0.1 (Student's t-test) 3) >0.1 (Student's t-test)
Number of painful episodes (median, range)	4.5 (0-13)	5 (0 to 14)	> 0.1 (Mann-Whithney test)
Post operative fluids: 1) Postoperative fluid and feed in first 24 hours, mean ml/kg (SD*) 2) number requiring postoperative fluids	1) 147 (55) 2) 9	1) 59 (33) 2) 0	1) Difference of means (95% CI*) 88 (61.3 to 114.9) 2) Not assessable

SD= standard deviation, CI=confidence interval Source:
Hughes (2013)

Table 3 Cup versus spoon during the 24-hour postoperative feeding period following surgical repair of cleft palate

	Cup feeding	Spoon feeding	Test statistic
Variables related to feeding technique: 1) coughing episodes during food administration (n Yes, %) 2) Choking during food administration (n Yes, %) 3) food escape by the commissure (n Yes, %)	1) 4 (5%) 2) 5 (6%) 3) 67 (76%)	1) 0 2) 1 (1%) 3) 52 (59%)	1) 0,121 (Fisher exact test) 2) 0,211 (Fisher exact test) 3) 0,024* (Fisher exact test)
Accepted volume, ml (median, range)	140.0	150.0	0,029* (Mann-Whitney test)

*** Significant association (p<0.05) Source:**
Trettene (2013)

Hughes (2013) showed that use of analgesia and the number of painful episodes was similar among the tube group (n=18) and the oral food group (n=23) within 24 hours post-surgery. However, the received amount of fluid food volume was higher in the tube feeding group, with less often need for intravenous fluid (Duarte, 2016).

Trettene (2013) showed that the spoon technique (n=88) caused less food escape and a higher volume of food received than the cup technique (n=88) within 24 hours post-surgery. It is unclear from this study if the food given with the cup was a different (thinner) consistency than the food with the spoon (Duarte, 2016).

From these studies it remains unclear which food consistency is most effective in week 3 to 6 post surgery, because this was not assessed (the studies did not meet the PICO). It also remains unclear if the food consistency differed among the nasogastric/oral feeding and cup/spoon feeding.

When nasogastric and oral feeding are compared in the first 24 hours, the nasogastric tube led to a higher postoperative fluid volume, however the number of painful episodes and need for analgesia was comparable. How often the tube itself led to pain, discomfort or damage to the repair was not assessed, but one case in which the tube had to be removed due to discomfort was described. Some infants (poor feeders for example) might benefit from nasogastric feeding, but the study of Hughes (2013) does not provide any selection criteria.

When cup and spoon feeding are compared, spoon feeding led to a higher amount of volume accepted and less food escape through the commissure. It could be hypothesized that soft food with the spoon is easier to consume, with less chances for leakage, swallowing or processing problems, than fluid food.

Both studies had a low methodological quality and a small sample size, so results should be interpreted with caution.

Palate repair and influences on eating function
One retrospective single center study from Japan (Fujikawa, 2016) was found that assessed the impact of

palate repair surgery on eating function: the amount of a whole meal that was consumed and the food type (fluid food, paste food, soft food and others). Nurses recorded the amount of food intake during the hospital period, and the data was retrieved from medical records. The protocol was made so that patients began with drinking water and taking fluid food and work TOwARDS eating food pastes and soft food by postoperative day 7.

A total of 19 patients participated in the study. All patients underwent push back palatoplasty.

The results show that the eating rate increased during the first 6 postoperative days and then stabilized. The amount of fluid foods and pastes decreased over time, and the amount of soft foods and other foods increased. Unfortunately, the study did not assess the 3 to 6 weeks post-surgery period. However, because palatoplasty greatly influences eating function, it could be expected that the energy intake remains insufficient for a longer period.

In case soft food is encouraged, it could be predicted the amount of fluid food and pastes will decrease, however this is largely speculative. From the analysis of Fujikawa (2016) it is also difficult to predict which food types are benefitting patients most in the 3 to 6 weeks post procedure. Because of the lower amount of food intake, and the lower nutritional value of fluid food and food pastes, the authors (Fujikawa 2016) recommend developing a new soft food type which minimizes palatal stress for postoperative cleft management. This study had a low methodological quality and limited amount of study participants, so results should be tasks with caution.

Bone graft
No studies were found that assessed bone graft and the impact of different food types or feeding methods.

Advantages and disadvantages of the feeding methods
Infants and children are very susceptible to problems of nutrition. In comparison with adults, they have lower percentages of muscle mass and fat and therefore have fewer caloric reserves in combination with a higher resting energy metabolism. Children are in a growth and developmental phase, with nutritional requirements that are greater and clearly different compared to those of adults and that vary according to the stage of growth. In sick and hospitalized children, malnutrition is associated with increased risk of infection, delayed wound healing, longer hospital stay, and increased morbidity and mortality (Joosten, 2017). In children with cleft lip/palate, feeding is an immediate concern. There is evidence of delay in growth of these children as compared to those without clefts, especially if these were associated with a syndrome or anomaly (Bessell, 2011). For example: Pandya (2001) found an incidence of failure to thrive in Pierre Robin patients or 100%. Therefore, in these children it is very important to evaluate the nutritional status and achieve optimal growth prior to and after surgery. If needed, a dietician or pediatrician should be consulted.

Operations in the mouth such as in cleft surgery might have significant impact in the intake of food and sometimes even fluids. Apart from the effect on general wellbeing of the child and his or her parents, food and drinks are crucial for proper wound healing. A balanced and clear protocol for postoperative feeding and feeding methods is therefore important. Unfortunately, the literature shows very little to no evidence for

clean food (soft versus solid) or feeding methods in the postoperative period. What we do know is that changes in food or feeding methods, either because the patient cannot or may not eat the food he or she is accustomed to, can lead to stress and loss of weight (Matsunaka, 2015; Madhoun, 2020).

Especially in young children minimizing crying is considered to be the important factor in avoiding tension on the surgical wound. For this reason, the use of a pacifier - to prevent crying - should be allowed as long as the tip of the pacifier does not reach the repair. Changes in feeding methods seems to stress the infants and may cause them to cry, which places tension on the wound (Matsunaka, 2015).

It is assumed that normal feeding with solid food may cause mechanical damage to the wound, but no evidence was found in the literature that endorses this idea. Cohen (1992) conclude in a retrospective analysis of two non-solid food feeding protocols, i.e. tube and syringe feedings versus unrestricted bottle or breast feeding, that there were no wound complications in the unrestricted group. They conclude that immediate unrestricted feeding may be instituted safely, thus improving and simplifying postoperative management after repair.

In a prospective randomized study (Kim, 2009) the effect of bottle-feeding versus spoon feeding on early postoperative course after palatoplasty was evaluated. They concluded that bottle-feeding had no adverse effect on wound disruption or fistula formation. Although statistically insignificant, infants in the spoon- feeding group ingested a larger amount of food during the first 3 days and the need for sedatives was lower as compared to the bottle-feeding group. For this reason, it would be wise to encourage parents to introduce spoon feeding as normally advised from the age of 4 months on, to ensure that children can eat well from a spoon after surgery.

The large variation in feeding protocols in the Netherlands after cleft surgery seems to be based on assumptions rather than on scientific evidence. It is evident that a thorough oral hygiene post-surgery, a subject closely related to eating, is very important too. Cleaning the mouth and teeth after feeding might have a positive influence on the possible negative effects of certain food or fluids on the wound. Because this subject was not part of the clinical question, we did not investigate the role of oral hygiene, but we like to mention its importance and relation to feeding.

Values and preferences of patients and their parents or guardians

In our experience a stringent feeding protocol which states soft food for a couple of weeks after cleft surgery seems to be a rather big burden for the cleft patients and their parents. Especially after bone grafting the alveolar cleft the most important question for the children is often when they can start their normal food again. One of the Dutch cleft teams created therefore a cookbook, written by and for children with a cleft and supervised by students of dietetics. The aim was to create tasty recipes in accordance with a soft diet protocol (https://www.radboudumc.nl/expertisecentra/expertisecentra-zeldzame-aandoeningen/CLA/P/masterkoekies- cookbook).

One study included in the review of Duarte (2016) states that (little) children who got a gastric feeding tube for 24 hours postoperative needed less pain medication and were dismissed faster. Also, their parents seemed to be more relaxed because they had the feeling their child received enough food and pain

Medication (Kent, 2009). The possible adverse events of gastric feeding tube are problems with reintroducing oral intake, need for replacement, infections and it might be a burden for the child itself. In general, the nasogastric feeding tube does not seem to be standard practice in the Netherlands unless the oral feeding methods are not successful after a certain amount of time. To prevent mechanical damage to the wound by fingers of the child, it is common to provide arm splints in some countries (the USA for example). This is not routine In The Netherlands because it is believed to discomfort the child by the use of splints.

Costs/Finances

A soft feeding protocol in general does not lead to extra costs. In some occasions supplementary food (i.e. Nutridrink) or a nasogastric feeding tube at home can lead to extra costs which are usually covered by the health care insurance in the Netherlands.

Acceptance, feasibility and implementation

Because no scientific evidence was found to advise a stringent soft food protocol versus a normal diet after cleft surgery, the working group collected the feeding protocols after cleft surgery (especially palate and bone graft procedure) of all the cleft teams in the Netherlands. The large variation in feeding protocols in the Netherlands after cleft surgery seems to be based on assumptions rather than on scientific evidence.

Table 4 shows an overview of the feeding protocols after cleft surgery of all cleft teams in the Netherlands. The results are shown for: Closure of hard palate (palatoraphia anterior), pharyngeoplasty, and bone grafting procedure in cleft patients. Only the common recommendations of the different teams are shown. The working group used this overview and the consensus between the feeding protocols as a guidance for the recommendations of this protocol.

The working group created support from all cleft teams through the collection of al feeding protocol, which increases the feasibility of the recommendations. If necessary, adjust nutritional advice to the preferences of the patient within the possibilities of the various protocols used, which are important for recovery and well- being.

Table 4 Overview feeding protocols post cleft surgery of Dutch cleft teams (lip surgery excluded)

General recommendations post cleft surgery		
Always start with drinking water post-surgery		
Always rinse with water after eating		
Don't use a straw for drinking		
Do not put hard object into the mouth such as fork, fingers, hard / sharp food such as chips		
No indications to apply nasal gastric feeding tube as standard of care		
Surgery	**Age child at operation**	**Common recommendations for post-surgical feeding prot**
Bone grafting procedure	9 to 12 years	Start with drinking water, then only fluid drinking (tea, apple juice, milk etc.)
		Thicker whispers: Like yogurt, oatmeal, soup
		Soft food: Like bread without crusts, mashed food, pasta
		Do not bite or chew with front teeth
Palatorafia anterior	variation 3 months to 3 years	fluids (like apple juice, milk, water)
		smooth grinded food (yogurt, smoothies, Olvarit 4 months)
		mashed food (like bread without crusts, pasta)
		no fingers or pacifier or thumb sucking
		avoid orange juice and grapefruit juice
Pharyngoplasty	4 to 7 years	fluids (like apple juice, milk, water)
		mashed food (like bread without crusts, pasta)
		avoid orange juice and grapefruit juice

Rational

Based on the literature summary, the working group is unable to make a statement about the effect of soft food versus normal/ solid food after cleft surgery. Our recommendations are therefore mainly based on the corresponding recommendations in postoperative nutrition of the various cleft teams in the Netherlands and on the expert opinion of the working group members.

Background of the Substantiation

After a cleft palate operation (palate repair or palatoplasty or pharyngoplasty) or alveolar bone grafting the patient is advised to drink fluid or eat soft food. The most important reason is to avoid mechanical damage to the wound bed. Following an alveolar bone graft procedure, the idea is to avoid chewing force to the premaxilla bone or front elements. Following a palate repair procedure, the patient is often also advised to avoid citrus fruits.

Currently, there is no clear evidence for these nutritional instructions, such as the relation between nutrition and disturbance of the soft tissues and bone. Meanwhile, the effort for the child and his/her parents to follow the post operative instructions for feeding seems to be considerable. In addition, there is a lack of evidence and no consensus regarding the duration of the nutritional instructions.

Next to the discussion about the food consistency, there is a discussion about whether or not tube feeding is effective after a palate repair procedure and pharyngoplasty. This discussion is mainly between surgeons and pediatric nurses or pediatricians and a decision that is usually made on individual (patient) basis and team preferences. This is a sub question which could be interesting to consider.

Because of the fact that lip closure and closure of the soft palate are usually performed in young infants who are bottle or breast fed, these procedures were not included in this module.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of consuming soft food (e.g. liquid food, mashed food or tube feeding) versus solid/normal food after cleft palate repair, pharyngoplasty and bone grafting procedure for children with cleft alveolus and/or palate?

P: Patients after cleft palate repair, pharyngoplasty and bone grafting procedure between 6 months and 11 years old;
I: liquid food, mashed food or tube feeding (until 6 weeks post procedure);
C: solid/normal food (until 6 weeks post procedure);
O: No disturbed wound healing, enough food intake, no moving premaxilla, no fistulas.

Relevant outcome measures
The working group considered surgical wound healing and amount of food intake/nutritional status as critical outcome measures for decision making; and moving premaxilla and fistulas as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinical (patient) important difference for the dichotomous outcome measures; RR < 0.80 or > 1.25)

No a priori criteria were set for the continuous outcome measures because it largely depends on its context. Search and

select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms Until August 20th, 2020. The detailed search strategy is depicted under the Tab Methods. The systematic literature search resulted in 331 hits. Studies were selected based on the following criteria:

- Involving patients with a cleft palate procedure or bone graft procedure between 6 months and 11 years old.
- Comparing liquid food, mashed food or tube feeding with solid/normal food 3-6 weeks postoperatively. This module focuses on the nutritional advice in the first 3 to 6 weeks after a surgical intervention, because it is expected that patients can continue their habitual nutrition intake after 3-6 weeks.
- Assessments surgical wound healing and/or the amount of food intake or nutritional status.

A total of 25 studies were initially selected based on title and abstract screening. After reading the full text, 25 studies were excluded (see the table with reasons for exclusion under the tab Methods) and no studies were included.

Results

No studies were found that answered the question: What is the effect of offering soft food versus solid/normal food after a cleft palate or bone graft procedure for children with cleft alveolus and/or palate? In the justifications a descriptive overview can be found of indirect studies.

Reporting

Last reviewed: 26-11-2021 Last
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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Lip and palate closure in patients with schisis

This module is divided into the following sub-modules:

- Timing of lip and palate closure in cleft palate
- Technique of lip and palate closure in cleft palate

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Timing of lip and palate closure in patients with a CLA/P

Primary question

Which considerations (advantages and disadvantages) play a role in determining the moment of closing the lip, jaw and/or palate cleft in children with a (cheilognatho) palatoCLA/P?

Recommendation

The lip should preferably be closed surgically in the first 6 months of life.

Preferably close the palatum durum and palatum molle in the first year of life to ensure optimal speech.

Preferably only close the mole palate in the first year of life and the durum palate only later if the optimal possible growth of the maxilla is aimed for.

Define a preferred approach within the lip and palate closure sketch team to advise parents in decision making. Support decision-making through written or digital information material, see Prenatal Medical Counseling module.

Considerations

Level of evidence (timing of closure)
The overall level of evidence regarding the timing of lip and/or palate closure is very low. The literature about the timing of palate closure is fragmented, and studies report different outcomes measures. No studies were found that compared different moments of lip closure.

Advantages and disadvantages of the different protocols
Unfortunately, no conclusions can be drawn from literature regarding the timing of lip and (hard) palatal closure. The literature does not answer the vivid discussion among professionals concerning the disadvantage of late palatal closure on speech development or the disadvantage of early palatal closure on maxillary growth. So, unfortunately, an optimal or uniform protocol on timing of palatal closure cannot be proposed based on literature. A complicating factor to study the effects of timing of repair of is the fact that the skills of the surgeon are hard to measure but it is likely that these skills - including education, personal training, experience, workload, and working environment - are an important factor in the outcome. Also, a uniform and validated method to assess, quantify and document VPI is not available. Moreover, reliable, reproducible assessment of speech remains a challenging field. Comparable speech assessment requires both validated tools and systematic consensus training of the assessors, which is not always available. Therefore, calibration is a key element for possible future studies and trials, including the surgical part of any multicenter study.

In addition to timing there are two other factors relevant for lip and/or palatal closure, i.e., the technique of closure and the sequence of closure. The technique of closure is reviewed in module Technique of lip and/or palate closure. For this guideline the sequence of closure was not regarded as a key factor for long term

Outcome, but it is undeniable an important variable in many of the protocols of Dutch cleft teams. It therefore deserves attention.

The Scancleft studies show the most common used sequences of palatal closure. In Arm A and Arm B the lip and soft palate are closed first followed by the hard palate a later stage (In Arm A within 12 months). In arm C the lip is closed first and the whole palate is closed in one operation within 12 months of age. In Arm D the lip and hard palate (with a vomerine flap) are closed first, and the soft palate closed at a later stage but within 12 months after births. Another option is to close the soft palate first (as this is functionally the most important part of a full) and to close the hard palate and lip together in the second operation, also within 12 months of age. This sequence was popularized in France under guidance René Malek of and forms one arm in a RCT published by Richard (2006).

To make it more complex there is very limited evidence that it may be beneficial to adjust the protocol to the type of cleft, for example the width of the cleft. A study by Botticelli (2020) on a subgroup of the Scandcleft trials suggests that - from an orthodontic point of view - a wide posterior cleft might benefit from later hard palate closure. The thought of adjusting your protocol to the local situation sounds logic and surgeons do sometimes adjust the protocol in an individual case intuitively, but this is a complex area for research.
Numbers for trials become extremely small in most centers when adjusting to subphenotyping the cleft and/or calculating relative dimensions, such as the width of the cleft in relation to the available tissue on the palatal shelve. This is an interesting field, but it has no implications for this guideline at present.

The velopharyngeal competence composite score (VPC-sum) as used in the study of Lohmander (2017) provides an indication of the velopharyngeal function by hypernasality, audible nasal air leakage, weakness of pressure consonants, and posterior nonoral articulation. No statistically significant differences in VPC-Sum or in hypernasality were found between the arms (arm A versus arm B).

The Scandcleft trials are of interest regarding possible differences in outcome due to variation in the sequence of closure of the palate during the first year of life. Although it was not a clinical question, the sequence of closure was part of the literature search. The working group has looked critically at the results of the Scandcleft trials regarding differences between arm A, arm C and arm D and the RCT published by Richards in 2006. Kuseler (2020) did not find significant differences in facial growth between arm A, C and D at age 8 years and Edwards (2006) did not find differences between the two arms in his study regarding speech and growth age 4 to 7 years. Therefore, sequence of closure of a complete during the first year of life does not seem to affect speech and or growth at a later age.

Timing in the Netherlands:
According to the NVSCA website the treatment protocols of the Dutch cleft-teams can be summarized:

- All teams except 1 close the lip at 3-4 months of age, one team closes the lip at 6 months of age. All teams
- close the soft palate mostly in the second half of the first year of life.

Closure of the hard palate diverges from 3 months to 12 years of age and shows the largest discrepancy. Just in 2021 there

remains a scarcity of good studies. The available literature does not provide evidence for

one single optimal/ best protocol to close during the first year of life. Although the Scandcleft trials provide a lot of information, they show at the same time how difficult it is to design and run good prospective multicenter studies from birth to adulthood (Shaw, 2017).
The current revision of this module in the guideline therefore will not solve the practice variation between different cleft teams regarding the closure of clefts of the lip and/or palate. Therefore, we are unremittingly faced with different philosophies in examination and treatment of . Lack of consensus is most evident in the timing hard palate closure. However, modesty should suit the (Dutch) cleft-teams regarding their local protocols, customs of preferences due to this lasting knowledge deficit. Based on the literature there is no evidence one cleft team can state they have better protocol compared to another team. Cleft teams should support parents in offering a clear explanation of their treatment protocol. Furthermore, it is advisable to share the knowledge and experience among the Dutch cleft teams to make progress in cleft care.

Therefore, the working group advises each cleft team to develop and present a team preferred treatment protocol and to document the results carefully and systematically for internal quality control and external comparison.

Although not supported by clinical research:

1. The working group advises to close the cleft lip in the first 6 months of life, as it is common practice in the Netherlands. This will allow the lip to function properly when the child starts babbling in the second half of the first year of life.
2. The working group advises to close the soft palate before 12 months to allow velum function to develop normally as babbling progresses to words around 1 year of age.

This advise regards – in line with this CPG – only healthy non-syndromic children. Especially before the palate is closed any signs of Obstructive Sleep Apnea (OSA) should be ruled out taking a throurough anamnesis and
/ or observation. When in doubt it is advised to do sleep studies and / or to postpone the palate closure.

Values and preferences of patients and their parents or guardians
Parents can be confused by the variety of surgical protocols and (sometimes strong) opinions on treatment by teams or surgeons. They need unambiguous information and advice. Unfortunately, literature does not provide us with enough scientific evidence to support one of the protocols of timing of closure over the other. Adversely the experience of a surgeon and his/her preferences for a certain technique is essential for optimal results. We advise that each team presents clearly what their vision on timing of closure is, elaborated in a straightforward protocol.

Anesthesiology
Parents may have concerns about anesthesiology for their young children (<1 year). These concerns are considered and discussed in the clinical practice (https://richtlijnendatabase.nl/richtlijn/anesthesie_bij_kinderen/faciliteiten_bij_anesthesie_bij_kinderen.html). The recommendations of this guideline are leading for daily practice in the Netherlands.

Costs/Finances

In general, good results should be achieved in as little surgeries as possible in order to keep the burden on the child, the parents as low as possible, and to keep the health care system within acceptable finances. It is important to properly lay the surgical base in the first year of life, and to keep intermediate interventions during growth to a minimum. The final corrections can be made when the patients jaws finish their growth, whereby the patient can then assess and decide for himself or herself what he or she needs or what he or she considers to be desirable.

Acceptance, feasibility and implementation

There is still a lot of variation in surgical practice between the cleft teams, although there seems to be a trend TOwARDS early closure of the hard palate. Special interest groups within the NVSCA try to tackle this point.
Within these groups, knowledge is shared, and appointments are made to standardize clinical practice as much as possible.
In the Netherlands everyone has equal access to the cleft teams, so there will be no variation in accessibility of care. The different protocols of timing of lip and/or palate closure exist due to the experience, expertise and preferences of each surgeon and each cleft team. is important that the surgeon uses the (combination of different) technique(s) and the timing protocol in which he or she is most experienced in order to achieve the best result.

Rational

The literature did not show a clear preference for timing of lip and/or palate closure, nor clear advantages and disadvantages of early or late closure of the palate. There is no medical indication for early lip closure (before 6 months), it is the preference of parents and social acceptance to close the lip early. To allow proper function soft palate closure should be performed within the first year of life. When closing the palate any signs of Obstructive Sleep Apnea (OSA) should be ruled out taking a throurough anamnesis and / or observation.
When in doubt it is advised to do sleep studies and / or to postpone the palate closure.

A broad recommendation is given, partly due to the lack of scientific evidence, taking into account the experience and expertise of the cleft team.

Background of the Substantiation

In case of a cleft of the palate there is an abnormal connection between the nasal and oral cavities. The posterior part of the nasal and oral cavities merge in the oropharynx. Under normal conditions the soft palate functions as a valve, actively closing the nasal cavity from the oral cavity on demand. This is an essential function to build up pressure for speech and to create a vacuum, for example for feeding. Therefore, a cleft palate - Even if it is minor- causes functional impairment in drinking and speech.

Closure of the (soft and/or hard) palate intents to create a separation between the oral and nasal cavities to solve these problems. Evidently early closure aims to solve these problems faster compared to later closure. The plea for early closure is logical from a pure functional point of view. The problem with early closure relates to scar formation. Some degree of scar formation during surgical closure of the palate is inevitable, even with the best techniques and an experienced surgeon. Car formation however can cause disturbance of growth or

the upper jaw. It is thought that especially scar formation during closure of the hard palate is responsible for most of the noted growth disturbance. Early closure (<18 month) of the hard palate causes scar formation at a younger age and has therefore more time to affect growth of the maxilla compared with later closure.

Disturbed growth of the maxilla is not benign and leads to midface underdevelopment, class 3 malocclusion, and less prominence of the nose. Even the width of the upper jaw might stay small causing cross bite. These problems may require orthognathic surgery such as a Le Fort I osteotomy after growth has been completed around 18 years of age.

In summary: The classic teaching tells us that early closure favors function, late closure (especially of the hard palate) is better for growth, the holy grail being early closure without growth disturbance.

In view of the issues raised the timing of (partial) palatal closure seems important. Timing of closure of the cleft lip is less subject to debate. Lip closure does not seem to impair growth. Due to the esthetic importance the cleft lip is usually repaired in the first year of life, mostly in the first trimester after birth, frequently combined with primary correction of the nose (see module on cleft nose correction). Nevertheless, it is important to substantiate timing of lip closure with current literature.

This module does not address the timing of bonegrafting of the alveolar cleft. The focus is on soft tissue closure, achieving separation of the oral and nasal cavities.

Conclusions

1. Hard palate

1.1 Maxillary and midface growth (critical)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on maxillary and midfacial growth. *Resources: (Heliövaara, 2017; Heliövaara, 2019; Karsten, 2017; Karsten, 2020; Küseler, 2020;*

1.2 Speech (velopharyngeal insufficiency) (critical)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on speech. *Resources: (Lohmander, 2017; Richard, 2006; Willardsen, 2017; Williams, 2011)*

1.3 Aesthetics (patient, parent and/or doctor satisfaction) (critical)

- GRADE	There is no GRADE assessment possible due to lack of studies.

1.4 Hearing (important)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on hearing. *Resources: (Richard, 2006)*

1.5 Feeding capability (important)

- GRADE	There is no GRADE assessment possible due to lack of studies.

1.6 Post-operative complications (important)

Very low GRADE	The evidence is very uncertain about the effect of timing of hard palate closure on postoperative complications. *Resources: (Rautio, 2017; Reddy, 2018; Richard, 2006; Williams, 2011)*

2. Lip closure

- GRADE	There is no GRADE assessment possible due to lack of studies.

Summary of literature

Description of studies

A total of 12 RCT studies was included in this literature summary. Most included studies are part of the Scandcleft trials (Heliövaare (2017); Heliövaare (2019), Karsten (2017); Karsten (2020), Küseler (2019), Lohmander (2017), Rautio (2017), Willardsen (2017)). In these trials, lip and soft palate closure at 3 to 4 months, and hard palate closure at 12 months served as a common method in each trial (Arm A, n= 75).

Trial 1 compared arm A with hard palate closure at 36 months (arm B, n=73). Which is of interest for this module.
Trial 2 compared arm A with lip closure at 3 to 4 months and hard and soft palate closure at 12 months. Which is not included in the PICO.
Trial 3 compared arm A with lip and hard palate closure at 3 to 4 months and soft palate closure at 12 months.
Which is not included in the PICO.

The primary outcomes of the scandcleft trials were speech and dentofacial development, with a series of perioperative and longer-term secondary outcomes, perioperative complication rate, operation and hospitalization time, postoperative recovery and feeding, speech at 12 and 18 months and 3 years, symptomatic fistulae, hearing, burden of care, and parent satisfaction at age 5 years (till the age of 5 or 8).

Reddy (2018) describes a blocked RCT (not part of the Scandcleft trials) that compared a one-stage palatoplasty at age 12 to 13 months (group A) with a two-stage palatoplasty patients with soft palatoplasty at age 12 to 13 months and hard palatoplasty at age 24 to 25 months (group B). A total or 100 nonsyndromic

unilateral cleft lip and palate patients were included. The two groups were compared on fistula rates at 3 years and hypernasality at 6 years. In addition, both groups were compared with a control group of 20 noncleft controls on hypernasality at 6 years.

Richard (2006) describes an RCT in which the effects of operating the soft palate first (n=23, at follow-up 16) versus operating hard palate first (n=24, at follow-up n=19) on facial growth are studied in unilateral complete cleft lip and palate patients. The anterior operation consisted of a lip repair by Millard rotation advancement, a nasal correction using the McComb procedure and a hard palate repair by a single layer vomerine flap. The posterior operation consisted of a soft palate repair with medial von Langenbeck incisions. The two operations were undertaken three months apart with the first operation at 19 months of age. Preoperative maxillary models, speech and velopharyngeal function and ontological examinations were performed. Patients were followed until the age of four to six years.

WADA (1990) is a RCT that describes the effects of one-stage palatal closure (unilateral cleft n=14, bilateral n=8) versus two-stage palatal closure (unilateral n=16, bilateral n=7) in patients with uni- and bilateral cleft lip and palate. Also, the maxillary growth was compared with 11 healthy controls. Lip repair was performed at five months of age. One-stage repair was performed at 20 months using mucoperiosteal palatal pushback procedure. Two-stage repair was performed with primary veloplasty at 20 month and double overlap palatal hingeflap procedure at five years ten months. Maxillofacial cast models were examined. The children are followed until the age of ten years.

Williams (2011) describes a RCT in which different surgical techniques and different timings of surgery for cleft palate were compared in terms of speech outcome and risk of palatal fistulae in patients with a complete unilateral cleft lip and palate. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to one of eight groups: one of two different lip repairs (Spina versus Millard), one of two different palate repairs (von Langenbeck versus Furlow) and one of two different ages at time of palatal surgery (9 to 12 months versus 15 to 18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9 to 12 months (Spina - Furlow = 35, Millard - Furlow = 43, Spina - Langenbeck = 51, Millard - Langenbeck = 52) and 195 at 15-18 months (Spina - Furlow = 48, Millard - Furlow = 47, Spina - Langenbeck = 46, Millard - Langenbeck = 54). Children were followed for at least the age of four years.

Results

1. Hard palate

1.1 Maxillary and midface growth (critical)

The dental arch relationship, measured with GOSLON Yardstick score, in children at five and eight years old is shown in the studies of Heliövaara (2017) and Heliövaara (2019), respectively. Children at five years of age (n=74) receiving the repairing of hard palate at 12 months (arm A) had a mean index score of 2.86 (SD 0.94) and 5-years old children (n=68) receiving the repairing of hard palate at 36 months (arm B) had a mean score of 2.58 (SD 0.87). This difference was not significant (p=0.06). At the age of 8 years, children in arm A (n=72) had a mean score of 3.03 (SD 0.85) and children in arm B (n=73) had a mean score of 2.82 (SD 0.81), p=0,137.

Karsten (2017) and Karsten (2020) present the occlusion as outcome of hard palate closure, measured with the Modified Huddart and Bodenham index (MHB), in children at five and eight years old. The total MHB score is

sum of the anterior score and two posterior scores (cleft and non-cleft side) and ranges from +2 to -18). Children at the age of 5 in Arm A (n=75) had a mean total MHB score of -6.80 (SD 4.02) compared to 5-years old in Arm B (n=68) who had a mean total MHB score of -5.95 (SD 4.17). There was no significant difference between the groups: MD -0.86 (95% CI -2.21-0.50), p =0.21. Children at the age of 8 in Arm A (n=74) had a mean total MHB score of -9.57 (SD 5.53) compared to 8-years old in Arm B (n=73) who had a mean total MHB score of -8.51 (SD 5.67). There was no significant difference between the groups: MD -1.06 (95% CI -2.90- 0.78), p =0.26.

Maxillary growth in 8 years old children is reported by Küseler (2020). Maxillary growth was assessed by cephalometric angles SNA (angle between selle, nasion, and subspinal point) and ANB (angle between maxilla and mandible) using lateral cephalograms. The mean ANB was 2.88 (95% CI 1.68 to 4.07) in the 8 years old children of arm A (n=74) and the mean ANB was 3.55 (95% CI 2.44 to 4.67) in the 8 years old children of arm B (n=72), p=0.12 (95%CI −0.19 to 1.66). The mean SNA was 78.42 (95% CI 76.63 - 80,20) in the 8 years old children of arm A (n=74) and the mean SNA was 78.90 (95% CI 77.28 - 80,52) in the 8 years old children of arm B (n=72), p=0.41 (95% CI −0.69 to 1.69).

Richard (2006) describes that there was no significant difference in overall facial growth between the different types of palatal closure sequencing.

WADA (1990) reports that in unilateral cleft palate patient's maxillary growth after two-stage palatal closure was comparable to those of non-cleft controls regarding depth and height of the maxilla, while after one- stage closure aberrant maxillary development was observed. For patients with bilateral clefts, maxillary growth was similar in the one-stage and two-stage palatal closure groups.

Level of evidence of the literature

The level of evidence regarding the outcome maxillary and midface growth started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -1), the small study populations (imprecision, -1), and circumstantitness (-1).

1.2 Speech (velopharyngeal insufficiency) (critical)

Lohmander (2017) shows the effects of timing on the speech outcome hypernasality. Hypernasality was measured using two different methods: Nasometry (nasalance score) and perceptual analysis. In the study of Reddy (2018) the one-stage palatoplasty group (group A, n=50) had a mean nasalance score of 20.61 ± 9.23 percent and group B (two-stage palatoplasty, n=50) had a mean score of 16.77 ± 2.15 percent, which is a significant difference between the groups (p=0,006; 95% CI 1.16 to 6.53). The perceptual analysis of hypernasality did not show significant difference between the groups: group A had 18 patients with hypernasality on single words versus 20 patients in group B (p=0,837 and p=1,000 for single words and sentences respectively). Compared to the noncleft control group, group A had a significant higher score on hypernasality (p=0,001, 95% CI 2.05 to 7.52). There was virtually no difference in the mean nasalance scores for patients in group B and subjects in group C (p=0,088, 95%CI −0.14 to 2.02).

Richard (2006) reports that there was hypernasal resonance significantly enough to warrant surgery in five patients in the posterioir-anterior group and four in the anterior-posterior group. This difference was not statistically significant.

Willardsen (2017) evaluates the effect of timing on speech outcome in terms of consonant production, in children at five years old. The percent consonants correct (PCC) score showed a significant difference between the arms; a higher median PCC score in arm A compared to arm B (p=0,045). The median number of active cleft speech characteristics (cscs) was significantly higher in arm B compared to arm A (p=0,003).

Williams (2011) reports that of the patients operated early (9 to 12 months) 78% had hypernasality and 57% had nasal air emission versus 74% and 55% operated late (15 to 18 months respectively). The odds ratio for hypernasality was 1.46 (95% CI: -0.84 to 2.54, p=0.12) and for nasal air emission 1.16 (95% CI: 0.72 to 1.85, p=0.49) for patients operated early versus patients operated late.

Level of evidence of the literature

The level of evidence regarding the outcome measure speech started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -1), the small study populations (imprecision, -1), and indirect tness (-1).

1.3 Aesthetics (patient, parent and/or doctor satisfaction) (critical)

No studies were identified that met the inclusion criteria and reported esthetic results as an outcome measure.

Level of evidence of the literature

The level of evidence regarding the outcome measure feeding capacity was not assessed due to lack of studies.

1.4 Hearing (important)

Richard (2006) reports that there was no significant difference in hearing status between the patients in the posterior-anterior group and the anterior-posterior group.

Level of evidence of the literature

The level of evidence regarding the outcome measure speech started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -2), and the small study populations (imprecision, -1).

1.5 Feeding capability (important)

The outcome feeding capacity was not reported in the included studies.

Level of evidence of the literature

The level of evidence regarding the outcome measure feeding capacity was not assessed due to lack of studies.

1.6 Post-operative complications (important)

Rautio (2017) presents surgical results of the Scandcleft studies, including complications after the surgery; major dehiscence of the palate needing fistula repair and number of patients who needed VPI surgery at the age of 5 years and extended to the moment that the youngest patient in the study was 5 years old (with updating until 9 years). In arm A a total of 6 patients (8%), major dehiscence of the palate compared to a total of 4 patients (6%) in arm B (p=0.10). The number of patients who needed VPI surgery was 2 (3%) in Arm A compared to 1 patient (1%) in Arm B at the age of 5 years. After the extended period, a total of 18 patients (24%) needed VPI surgery in Arm A compared to 18 patients (26%) in Arm B.

Reddy (2018) reports four patients with fistula in the one-stage palatoplasty at age 12 to 13 months (group A, n=50), whereas in the two-stage palatoplasty two patients had fistulas: OR 2.1 (p = 0,409; 95% CI, 0,365 to 11.9).

Richard (2006) reports that there were 10 symptomatic fistulae in the anterior-posterior group and six in the posterior-anterior group (p> 0.05).

Williams (2011) describes that 44/181 patients operated early (9 to 12 months) developed a fistula, versus 37/195 in the late (15 to 18 months) operation group. The odds ratio for fistula formation in the early versus late group was 1.37 (95% CI: 0.84 to 2.22, p=0.21).

Level of evidence of the literature

The level of evidence regarding the outcome measure speech started at high as it was based on a RCT but was downgraded by three levels to very low due to study limitations (risk of bias, -2), and the small study populations (imprecision, -1).

2. Lip closure

No studies were found that compared lip closure before and after 3 months.

Level of evidence of the literature

The level of evidence was not assessed due to lack of studies.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of the timing of repairing cleft lip, alveolus and/or palate on maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction)?.

P: Patients with cleft lip, alveolus and/or palate;
I: Closing hard palate before 18 months/ closing lips before 3 months; C:
Closing hard palate after 18 months/ closing lips after 3 months;
O: Maxillary and midface growth, speech, hearing, feeding capability, postoperative complications (fistulae), and esthetics (patient, parent and/or doctor satisfaction).

Relevant outcome measures

The working group considered the following outcome measures as critical for decision making: Maxillary and midface growth, velopharyngeal insufficiency, and esthetics. The outcomes speech, hearing, feeding capability, and postoperative complications were considered as important outcome measures.

Studies should report at least one of the outcomes of interest: Esthetics (patient, parent and/or doctor satisfaction), maxillary and midface growth, and velopharyngeal insufficiency. For the outcome measure speech, a follow-up until at least the age of 4 years was deemed sufficient, and for outcome measure hearing a follow-up length of at least 1 year after surgery was deemed sufficient. When papers reported a shorter follow-up time they were excluded.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinical (patient) important difference for the dichotomous outcome measures; RR < 0.80 or > 1.25)

No a priori criteria were set for the continuous outcome measures because it largely depends on its context. If no information was available about the clinically important difference of the outcome measure, a difference of ten percent between the groups was defined as a minimally clinically important difference.

Search and select (Methods)

A previous systematic search was performed for the 2018 edition of the guideline in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and December 3rd, 2014. The initial search identified 516 references of which 40 were assessed on full text.. After assessment of full text, 22 studies were excluded, and 18 studies were included. To update the previous search, the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 15th of January 2020. The detailed search strategy is depicted under the Tab Methods. The updated systematic literature search resulted in 529 hits. Studies were selected based on the following criteria: Studies investigated patients with were selected if they compared two different moments in time for repairing . A total 22 studies (2 reviews and 20 randomized controlled trials (RCTs)) were initially selected based on title and abstract screening. After reading the full text, the 2 review studies were excluded (see the table with reasons for exclusion under the tab Methods), and 9 RCTs were included and added to the results of the RCTs from the previous search. RCT's provide a higher level of evidence, therefore the (reviews of) observational studies of the previous search were removed from the analysis (n=15).

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Technique of lip and palate closure in patients with a CLA/P

Primary question

Is there a preference for a surgical technique when closing the lip, jaw and/or palate cleft in children with a CLA/P?

Recommendation

During palate closure, position the palate musculature to a more anatomical position (connection in the median and more posteriorly) for a better speech result.

Use a palate closure (combination) technique(s) in which the surgeon is most experienced to minimize the risk of complications.

Use a lip closure (combination) technique(s) in which the surgeon is most experienced for optimal function and aesthetics results with minimal risk of complications.

Stimulate the discussion about the technique(s) and outcome measures in the CLA/P-surgeons *special interest groups* (SIG's) NVSCA)*.

**In doing so, aim for a nationwide uniform definition of which outcome measures for CLA/P surgery are measured and stimulate a national audit in which outcome measures are compared per protocol.*

Considerations

Level of evidence
The level of evidence regarding different techniques of lip and/or palate repair is limited. Overall, the literature is fragmented due to the number of different techniques and the use of different outcomes measures. The problem of a lack of uniform outcomes measures was also addressed in module Timing of closure.
Summarizing it can be stated that hard and soft palate repair with perfect unhampered growth and optimal speech without VPI remains the holy grail for which no perfect solution has been found so far.

For the future the choice of surgical technique ideally should take into account the subphenotype of the cleft, relevant genetic information and an estimate of the potential growth of the maxilla for each individual, but this has not reached clinical practice so far.

For lip closure, the evidence is uncertain about the effect the different techniques on esthetics and the other outcome measures were not described in the studies.
In addition, the level of evidence is hampered by the fact that the skill and experience of the surgeon plays an important role in all surgery related studies and no doubt also in closure techniques. Small – but perhaps important - technical variations between CentrEs and surgeons performing the same operation do exist (and are the driving force behind innovation). As a result, a von Langenbeck closure in the hand of

surgeon or centRE A might differ from the same operation by surgeon or centRE B. Even within CentrEs true calibration between surgeons is not something commonly done. This all makes measuring outcome and comparison of studies in this field quite complex and lowering evidence levels.

Advantages and disadvantages of the different techniques

Palatal closure techniques

This module concerns the techniques of lip and/or palate closure. There is a close relation to the module “Timing of lip and/or palate closure”. Unfortunately, literature does not show enough evidence to support certain techniques of palatal closure. However, we do some suggestions and give some tips in selecting a type of surgical technique.

The main used techniques of soft palate closure are straight midline closure of the mucosa with or without lateral relaxing incisions versus double opposing z-plasty according to Furlow. Both techniques are performed by experienced surgeons with acceptable results, but every technique has a learning curve. The advantage of the straight-line closure is its relative ease and it preserves the opportunity to do a second correction through the same scars. The advantage of the Furlow technique is transposition of mucosa increasing the length of the soft palate but at the expense of tissue in width. Therefore, the Furlow technique is less favorite for wider palatal clefts with a higher rate of fistula formation (Williams, 2011). Position of the scars makes revision surgery more complicated in the Furlow technique.

Attention should be payed to reconstruction of the muscular sling of the levator veli palatini muscle. Sommerlad (2002) describes many details of this muscular repositioning. The Furlow double opposing z-plasty automatically creates the muscular sling. When a straight midline closure technique of the mucosa is used, separate attention for muscle positioning is indispensable.

Frequently used techniques to close the hard palate are the vomer flap (nasal layer only closure), mucoperiosteal flaps axially based on the great palatinal artery or anteriorly and posteriorly based leaf-flaps (Von Langenbeck) and buccal transposition flaps. The advantage of the vomer flap technique is that no scar tissue is made on the palatal bone, which may impair outgrowth of the maxilla. However only the relative thin nasal mucosa is closed and therefore more fragile. The mucoperiosteal flaps are thicker and firmer but require an extensive dissection from the bone which might inhibit full growth of the palatal bone. When the mucoperiosteal flaps are used simultaneous closure of the nasal palatal mucosa can be performed, resulting in a more secure double layer closure. The mucoperiosteal flap technique enables simultaneous closure of soft and hard palate. The advantage of the buccal flap technique is adding of tissue and therefore less dissection of the palatal bone. It can be used for nasal and oral layer closure. Disadvantage is scar formation of the buccal mucosa, it is more time consuming and might need additional surgery on the pedicle of the flap.

Lip closure techniques

Many lip closure techniques are described. Millard, Fisher and straight-line closure are favorite. Unfortunately, literature does not show enough evidence to support certain techniques of lip closure. However, we will do some suggestions in selecting a type of surgical technique. The straight-line technique gives good position of the scar in the -line but lengthening is limited. Straight line closure seems more applicable to incomplete

clefts of the lip. Fisher and Millard give better lengthening but a more extensive scar due to z-plasties. Many surgeons have their own variations on those basic techniques. In this context it should be mentioned there is no consensus how to rate the esthetic outcome of lip and nose after closure.

In conclusion, none of the mentioned surgical techniques seems to surpass the other, but experience of a surgeon with a certain technique is essential for optimal results.

Values and preferences of patients and their parents or guardians

Parents can be confused by the variety of surgical techniques and (sometimes strong) opinions on treatment by teams or surgeons. They need unambiguous information and advice. Unfortunately, literature does not provide us with enough scientific evidence to support one technique of surgical treatment for over the other. Adversely the experience of a surgeon with certain techniques is essential for optimal results. We advise that each team presents clearly what their vision on treatment is, elaborated in a straightforward protocol. Each protocol preferably illustrated by instructive photos and comprehensive movies.

Costs/Finances

In general, good results should be achieved in as little surgeries as possible in order to keep the burden on the child, the parents as low as possible, and to keep the health care system within acceptable finances. It is important to properly lay the surgical base in the first year of life, and to keep intermediate interventions during growth to a minimum. The final corrections can be made when the patient has grown out, whereby the patient can then assess and decide for himself or herself what he or she needs or what he or she considers to be desirable.

Acceptance, feasibility and implementation

There is still a lot of variation in surgical practice between the cleft teams, although a change seems to take place. Special interest groups within the NVSCA try to tackle this point. Within these groups, knowledge is shared, and appointments are made to standardize clinical practice and to measure outcomes in a uniform way as much as possible. In the Netherlands everyone has equal access to the cleft teams, so there will be no variation in accessibility of care. The different techniques are also equally feasible to perform, each surgeon has his own experience and expertise. It is important that the surgeon uses the (combination of different) technique(s) in which he or she is most experienced in order to achieve the best result.

Rational

The literature shows that there is no clear preference for a technique, several techniques could be used for lip and palate closure. There are no obvious advantages and disadvantages to the various techniques. A broad recommendation is made, partly due to the lack of scientific evidence, taking into account the experience and expertise of the surgeon.

Background of the Substantiation

The presence of a cleft lip, alveolus and/or palate () causes an abnormal appearance, the inability to

close the lip and/or the inability to separate the nasal cavity from the oral cavity. A cleft palate causes feeding and speech problems. A cleft lip is often associated with abnormalities of the nose affecting appearance and causing functional problems. A cleft in the alveolar arch results in orthodontic and dental abnormalities. The different phenotypes cause permanent stigmata. The aim of the multidisciplinary treatment of is to efficiently reduce these problems to a minimum.

Surgery that closes the lip and/or the palate (soft and/or hard) aims to improve function and apperance, and at the same time should not impair growth and induce as few new problems as possible. Many different techniques have been described over time. It is important to know which technique gives the best results in the short term and the long term. While writing the previous edition of the guideline (2018), it appeared that there was a shortage of prospective and randomized studies.

Conclusions

1. Soft palate

1.1 Outcome measure speech (critical)

Very low GRADE	The evidence is uncertain about the effect of different techniques of soft palate repair on speech related outcomes like hypernasality and nasal emission. *Resources: (Abdel-Azziz, 2011; Ganesh, 2015; Henkel, 2004; Williams, 2011)*

1.2 Outcome measure hearing (critical), 1.3 Outcome feeding capability (critical) and 1.6 Outcome measure esthetics (important)

- GRADE	There is no GRADE assessment due to lack of randomized studies.

1.4 Outcome measure maxillary and midface growth (important)

Very low GRADE	The evidence is uncertain about the effect of the vomer flap technique (one-layer closure) compared to the two-flap technique on dental arch relationship (measured at the age of mixed dentition). *Resources: (Ganesh, 2015)*

1.5 Outcome measure postoperative complications (important)

Very low GRADE	Postoperative complications, in the sense of fistulae, may occur using different techniques, however, the evidence is uncertain about the effects of the techniques on the incidence and type of fistulae. *Resources: (Abdel-Azziz, 2011; Ganesh, 2015; Henkel, 2004; Williams, 2011)*

2. Hard palate

2.1 Outcome measure speech (critical), 2.2 Outcome measure hearing (critical) 2.3 Outcome feeding capability (critical) and 2.6 Outcome measure esthetics (important)

- **GRADE**	There is no GRADE assessment due to lack of studies.

2.4 Outcome measure maxillary and midface growth (important)

Very low **GRADE**	The evidence is uncertain about the effect of one-flap versus the two-flap techniques for closing the hard palate at about 3 months of age on dental arch relationships and maxillary arch dimensions after 5 years. *Resources: (Rossell-Perry, 2017)*

2.5 Outcome measure postoperative complications (important)

- **GRADE**	There is no GRADE assessment due to events. *Resources: (Rossell-Perry, 2017)*

3. Lip closure

3.1 Outcome measure speech (important), 3.2 Outcome feeding capability (important), 3.3 Outcome measure maxillary and midface growth (important), 3.4 Outcome measure postoperative complications (critical)

- **GRADE**	There is no GRADE assessment due to lack of studies.

3.5 Outcome measure esthetics (critical)

Very low **GRADE**	The evidence is very uncertain about the effect of different techniques of lip repair on esthetics. *Resources: (Chowdri, 1990; de Silva Amaratunga, 2004; Williams, 2011)*

Summary of literature

1. Palatum molle/ soft palate

Description of studies

A total of four randomized controlled trials (RCTs) were included: Abdel – Aziz (2011); Henkel, (2004); Ganesh (2015); Williams (2011).

The study of Abdel-Aziz and Ghandour (2011) is a RCT that compares the effects of the Furlow double opposing Z-plasty (n=22) and the Wardill – Kilner V-Y (n=24) pushback technique in terms of velopharyngeal outcome and speech in patients with a cleft of the palate and no other congenital anomalies. Age at surgery was 11-36 months. All cases were followed for at least 1 year. Flexible nasopharyngoscopy and perceptual speech resonance evaluation were used to assess the velopharyngeal closure and speech outcome respectively.

The study of Henkel (2004) is a RCT in which the effects of soft palate closure using the wave-line technique in

the intravelar veloplasty (n=12) are compared to the classic intravelar veloplasty (n=12) in terms of speech outcomes in patients with complete cleft of the soft palate. Patients were randomly assigned to one or the other group following a previously determined succession. Surgery was performed at the age of 10-12 months. Speech was investigated at the age of 4 years by a speech pathologist blinded for the technique.

Ganesh (2015) describes a RCT to evaluate the effects of two different surgical protocols (vomer flap and separate soft palate closure versus two-flap technique) on dental arch relationship, speech outcomes and the occurrence of fistula during mixed dentition (7-10 years). Out of 200 patients recruited only 179 patients completed the treatment for lip and palate repair. Out of those 179 patients, 91 patients were allocated to the VF Group and 88 patients to the TF group. However, only 85 patients in total were seen at the follow up during the period of mixed dentition. In the vomer flap group (n=40), the cleft lip was repaired using the Millard technique along with nose correction. After 6 months, soft palate repair was carried out with sharp separation of the muscle fibers from the enveloping oral and the nasal mucosa and from the hard-palatal shelves. The tensor tendon was released just medial to the hamulus, followed by retro positioning and plication of muscle bundles along the midline. In the two-flap group (n=45), cleft lip was repaired by the Millard technique with nose correction, and anterior palate repair up to the incisor foramen. Six months later, the palate was repaired with two-flap palatoplasty. Both in the two-flap group and the vomer flap group the same technique of soft palate closure was followed. Greater part of the velar muscles (Tensor veli palatini & Levator veli palatini) was dissected free from its abnormal attachments followed by recreation of the muscular sling, retro positioning, and plication of muscle bundles along the midline. All operations were performed by the same plastic surgeon.

Williams (2011) describees a rct in which different surgical techniques and different timings of surgery for complete cleft palate were compared in terms of speech outcome and risk of palatal fistulae in patients with a complete unilateral cleft lip and palate. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to 1 of 8 groups: 1 or 2 different lip repairs (Spina versus Millard), 1 or 2 different palate repairs (von Langenbeck versus Furlow) and 1 of 2 different ages at time of palatal surgery (9-12 months versus 15-18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9-12 months (Spina – Furlow = 35, Millard – Furlow = 43, Spina – Langenbeck = 51, Millard – Langenbeck = 52) and 195 at 15-18 months (Spina – Furlow = 48, Millard – Furlow = 47, Spina – Langenbeck
= 46, Millard – Langenbeck = 54). Children were followed for at least the age of 4 years.

Comparison 2. Palatum durum/ hard palate

Description of study

One study is included in this literature summary that described hard palate surgery (Rossell-Perry, 2017).

The article of Rossell-Perry (2017) a prospective, randomized, single-blind controlled trial describes the effect of relaxing incisions on maxillary growth after primary palatoplasty in patients with unilateral cleft lip and palate at the age of five. Cleft lip repair was performed in all patients at approximately 3 months of age using the two-flap (n=72) or one-flap method (n=70) according to their usual surgical protocol: upper rotation advancement plus double unilimb Z-plasty or triple unilimb Z-plasty. The one-flap palatoplasty differed from the two-flap technique using a relaxing incision on the cleft side only. Extension of the subperiosteal dissection was the same in both groups. The soft palate surgical treatment was likewise identical with both

techniques. All operations were performed by the same plastic surgeon. Dental arch relationships and maxillary arch dimensions were evaluated at the age of five. The dental arch was rated from 1 ("excellent") to 5 ("very poor") and maxillary arch was evaluated as (1) intercanine distance = distance between the canine mesiobuccal cusp tips, (2) intermolar distance = distance between the second molar mesiobuccal cusp tips, and (3) maxillary length = distance in the midline from a point between the incisors to the posterior border of the maxilla.

Comparison 3. Lip closure

Description of studies

Three randomized studies comparing different lip closure techniques were identified; (Chowdri, 1990; de Silva Amartunga, 2004, Williams. 2011).

Chowdri (1990) is a randomized comparative study performed in India in which rotation advancement lip repair as described by Millard (n=58) is compared to triangular flap lip repair as described by Randall (n=50) in terms of esthetic results and complications. Age at lip repair was 3 years. Patients were followed for 1 to 6 years. Esthetics were evaluated independently by 3 examiners, each scoring surgical results on a 0 to 10 scale for 10 aspects of lip (50 points) and nose (50 points), making a total assessment of 100 points for the 10 components studied.

De Silva Amaratunga (2004) describes an RCT in which the esthetic results of unilateral lip repair are compared for Millard's method (n=18), Cronin's method (n=21) and a combination of the two methods (n=20). Lip repair was performed at the age of 2 to 6 months. The results of the repair were assessed 3 months after surgery. Esthetic results were assessed using the Cleft Lip Component Symmetry Index (0 to 100, with 100 points indicating perfect symmetry).

Williams (2011) describes a RCT which is mentioned in the section on palatal closure above. In this study not only the surgical techniques for closure of palate where compared but also the surgical closure of lips with 2 different techniques. A 2x2x2 factorial clinical trial was used in which each subject was randomly assigned to 1 of 8 groups: 1 or 2 different lip repairs (Spina versus Millard), 1 or 2 different palate repairs (von Langenbeck versus Furlow) and 1 of 2 different ages at time of palatal surgery (9 to 12 months versus 15 to 18 months). All surgeries were performed by the same 4 surgeons. A total of 181 patients were operated at 9 to 12 months (Spina - Furlow = 35, Millard - Furlow = 43, Spina - Langenbeck = 51, Millard - Langenbeck = 52) and 195 at 15 to 18 months (Spina - Furlow = 48, Millard - Furlow = 47, Spina - Langenbeck = 46, Millard - Langenbeck = 54). Children were followed for at least the age of 4 years.

Results

The different techniques and the different outcomes in the included studies are presented in Table 1.

Table 1 different comparisons and different techniques in the included studies

Study	**Techniques**		**Results**	
	Experimental group	**Control group**	**Experimental group**	**Control group**

1. Soft palate				
Abdel-Azziz, 2011	Furlow double opposing Z-plasty (n=22)	Wardill – Kilner V- Y pushback technique (n=24)	Speech Nasality: 0.88 ± 1.01 Nasal emission: 0.92 ± 1.1 Complications: Fistulae N=2	Speech Nasality: 0.27 ± 0.55 Nasal emission: 0.36 ± 0.73 Complications: Fistulae N=0
Ganesh, 2015	Vomer flap (Millard technique for the lip along with correction nose) (n=40)	Two-flap technique for the whole palate (Millard technique with nose correction, and anterior palate repair up to the incisor foramen) (n=45)	Speech Hypernasality Normal: 11.8% Mild: 70.6% Moderate: 17.6% Weak oral pressure words: 41.2% sentences (present): 41.2% Maxillary and midface growth dental arch relation: 2.15 (0,662)	Speech Hypernasality Normal: 20.5% Mild: 76.9% Moderate: 2.6% Weak oral pressure words: 15.4% sentences (present): 15.4% maxillary and midface growth Dental arch relation: 2.49 (0,757)
Henkel, 2004	wave-line technique in the intravelar veloplasty (n=12)	classic intravelar veloplasty (n=12)	Speech Compensatory grimacing when speaking: 1/12 (α-ι) test negative: 12/12 Sounds: /l/, /n/, /d/, /t/ normal: 6/10 Sounds /z/, /s/ normal: 6/10 Complications 1 patient with wound dehiscence in the oral mucosa	Speech Compensatory grimacing when speaking: 8/12 (α-ι) test negative: 8/12 Sounds: /l/, /n/, /d/, /t/ normal: 3/12 Sounds /z/, /s/ normal: 4/12 Complications No complications

Williams, 2011	Spina-Furlow 9-12 months (n=35) Spina – Langenbeck 9-12 months (n=51) Spina-Furlow 15-18 months (n=48) Spina – Langenbeck 15-18 months (n=46)	Millard -Furlow 9-12 months (n=43) Millard – Langenbeck 9-12 months (n=52) Millard – Furlow 15-18 months (n=47) Millard – Langenbeck 15-18 months (n=54)	Speech Hypernasality (von Langenbeck versus Furlow) OR 0.54 (95% CI: 0.31 – 0.95) p=0,014 Nasal air emission (von Langenbeck versus Furlow) OR: 0.72 (95% CI 0.45 – 1.15) p=0.12 Complications In total 37/269 (14%) patients operated by von Langenbeck developed fistula, versus 44/190 (23%) in the Furlow operation group. The odds ratio for fistula formation in the von Langenbeck versus the Furlow group was 1.93 (95% CI: 1.12 – 3.14, p=0,008).	
2. Hard palate				
Rossell-Perry, 2017	Two-flap upper rotation advancement plus double unilimb Z- plasty or triple unilimb Z- plasty (n=72)	one-flap upper rotation advancement plus double unilimb Z-plasty or triple unilimb Z-plasty and use of a relaxing incision on the cleft side only (n=70)	maxillary and midface growth 5-year-olds' index: 2.57 ± 1.08 -	maxillary and midface growth 5-year-olds' index: 2.80 ± 1.91
3. Lip closure				
Chowdri, 1990	Millard (n=58)	triangular flap lip repair as described by Randall (n=50)	Esthetics Lip: 38 ± 5 (possible range 0-50) Nose: 34 ± 4 (possible range 0-50) Lip + Nose: 71 ± 10 (possible range 0-100)	Esthetics Lip: 39 ± 5 (possible range (0-50) Nose:34 ± 4 (possible range 0-50) Lip + Nose: 73 ± 12 (possible range 0-100)

The Silva Amartunga, 2004	Millard's method (n=18)	Cronin's method (n=21) combination of the two methods (n=20)	Esthetics Cupid's bow height 77 Vermillion height: 87 Nostril height symmetry: 93 Nostril width: 96	Esthetics Cupid's bow height Cronin 86 Combined: 87 Vermillion height: Cronin: 97 Combined: 97 Nostril height symmetry: Cronin: 93 Combined: 92 nostril width: Cronin: 99 Combined: 95
Williams, 2011	See above			

1. Palatum molle/ soft palate

1.1 Outcome measure speech (critical)

Four studies (Abdel-Azziz and Ghandour (2011); Ganesh (2015); Henkel (2004); Williams (2011)) assessed speech. Due to heterogeneity of the different techniques evaluated in the studies and the different outcome measures, it was not possible to pool the data.

Abdel-Azziz and Ghandour (2011) described in 46 patients that velopharyngeal closure and speech outcome were statistically better after Furlow Z-plasty than after the V-Y pushback procedure. Auditory perceptual assessment for nasality was 0.88 ± 1.01 in the Furlow group and 0.27 ± 0.55 in the V-Y pushback group (p=0,035). Nasal emission was 0.92 ± 1.1 in the Furlow group versus 0.36 ± 0.73 in the V-Y pushback group (p=0,049). Globe articulation was 1.13 ± 1.04 in the Furlow group and 0.50 ± 0.74 in the V-Y pushback group (p=0,029). There was no statistically significant difference in pharyngealization of fricatives and speech intelligibility between the groups.

Ganesh (2015) reported speech outcomes of patients receiving vomer flap (VF) technique or two-flap technique (TF). In the VF group of 91 patients 36 needed releasing incisions. It was observed that the researchers were able to achieve less posteriorization of the velum in VF group when compared to the TF group (personal comment author upon e-mail request from working group May 2020). The results of the speech outcomes were obtained from only 34 patients in the VF group and 39 in the TF group, for various reasons. The results showed that 11.8% of patients in the vomer-flap group had normal resonance and 17.6% had moderate hypernasality. In the two-flap group 20.5% of patients had normal resonance and 2.6% showed moderate hypernasality, resulting in a RR of 6.88 (95% CI 0.87 to 54.35) for moderate hypernasality. Weak oral pressure consonants were perceived in 41% and 15% of the vomer flap and two-flap group, respectively (RR 2.68 (95% CI 1.16 to 6.19)).

Henkel (2004) showed in 24 patients that compensatory grimacing when speaking was observed in 1/12 patients in the wave-line veloplasty group versus 8/12 in the classic intravelar veloplasty group (p<0.05). A sound difference was observed in speech with a closed and open nose in 12/12 of the wave-line veloplasty group and 8/12 in the classic intravelar veloplasty group (p<0.05). Articulation of alveolar sounds was judged normal in significantly more subjects in the wave-line veloplasty group (6/10 (2 children too playful for examination)) versus the classic intravelar veloplasty group (3/12, p<0.05). They concluded that the waveline technique seems to be superior, however group size is small.

Williams (2011) reports in 376 subjects that patients operated using the von Langenbeck technique had an 0.54 OR (95% CI 0.31 to 0.95, p=0,014) for hypernasality and a 0.72 OR (95% CI: 0.45 to 1.15, p=0.12) for nasal air emission when compared to the Furlow technique.

Level of evidence of the literature

The level of evidence regarding the outcome measure speech started at high as it was based on randomized controlled trials. The level of evidence was downgraded by three levels to very low due to the risk of bias (-1, concealment allocation) and limited number of included patients (-2, imprecision).

1.2 Outcome measure hearing (critical)

The outcome hearing was not reported in the included studies.

Level of evidence of the literature

The level of evidence regarding the outcome measure hearing was not assessed due to lack of studies.

1.3 Outcome feeding capability

The outcome feeding capacity was not reported in the included studies.

Level of evidence of the literature

The level of evidence regarding the outcome measure feeding capacity was not assessed due to lack of studies.

1.4 Outcome measure maxillary and midface growth (important)

The dental arch relationship was measured by Ganesh (2015) with GOSLON scores; 1: Good growth - 5: Very poor growth. GOSLON scores of the 40 patients in the vomer flap group and 45 patients in the two-flap group were based on the intraoral digital photographs examined by a surgeon and an orthodontist, who were not members of the cleft team. These photographs were tasks during regular follow-up through the period of mixed dentition (age range 7 to 9 years old). The mean GOSLON score in the vomer flap group was lower than the GOSLON score in the two-flap group (mean difference = -0.34 (95%CI -0.64 to -0.04). In the vomer flap group, 70% of the patients demonstrated good growth (GOSLON scores 1 and 2) and 30% revealed adequate growth (GOSLON score 3). In the TF group, 54% of the patients displayed good growth, 37.7% had the adequate growth category, and 8.8% had poor growth (GOSLON score 4). None of the patients from either group were found to have very poor GOSLON scores (GOSLON score 5).

Level of evidence of the literature

The level of evidence regarding the outcome maxillary and midface growth started at high as it was based on a randomized controlled trial. The level of evidence was downgraded by three levels to low due to loss to follow up (-1, risk of bias), and the small study population and crossing the borders of clinical relevance (-2, imprecision).

1.5 Outcome measure postoperative complications (important)

Four studies (Abdel-Azziz and Ghandour (2011); Ganesh (2015); Henkel (2004); Williams (2011)) assessed postoperative complications. Due to heterogeneity of the different techniques evaluated in the studies, it was not possible to pool the data.

Abdel-Azziz (2011) reports that in total 0/22 fistulas were found in the Furlow group versus 2/24 in the V-Y pushback procedure group (no p-value reported).

Ganesh (2015) reported that palatal fistula appeared only in one patient in the vomer flap group (n=40) and did not appear in the two-flap group (n=45).

Henkel (2004) reports that 1 patient in the wave-line group developed wound dehiscence in the oral mucosa that healed secondarily without complications (p-value not reported). All other patients healed without complications.

In Williams (2011) only fistula rates were compared and were found not to be different between the Spina and Millard repair technique. In total 37/269 (14%) patients operated by von Langenbeck developed fistula, versus 44/190 (23%) in the Furlow operation group. The odds ratio for fistula formation in the von Langenbeck versus the Furlow group was 1.98 (95% CI: 1.16 to 3.07, p=0,010).

Level of evidence of the literature

The level of evidence regarding the outcome postoperative complications started at high as it was based on randomized controlled trials. The level of evidence was downgraded by three levels to very low due to the risk of bias (-1, concealment allocation) and limited number of included patients (-2, imprecision).

1.6 Outcome measure esthetics (important)

The outcome esthetics was not reported in the included studies.

Level of evidence of the literature

The level of evidence regarding the outcome measure esthetics was not assessed due to lack of studies.

2. Palatum durum / hard palate

2.1 Outcome measure speech (critical), 2.2 Outcome measure hearing (critical), 2.3 Outcome feeding capability (critical), and 2.6 Outcome measure esthetics (important)

These outcome measures were not reported in the included studies. Level of

evidence of the literature

The level of evidence regarding the outcome measures speech, hearing, feeding capability, and esthetics were not assessed due to lack of studies.

2.4 Outcome measure maxillary and midface growth (important)
Rossell-Perry (2017) reported dental arch relationships and maxillary arch dimensions after 5 years. Dental arch relationships were assessed using the 5-year-olds' index ranging from 1 (excellent dental arch relationship) to 5 (very poor dental arch relationship). The mean score for the 5-year-olds' index was 2.57±1.09 in the two-flap technique group (n=72) and 2.80±1.91 in the one-flap technique group (n=70); these scores were not significantly different between the groups. None of the patients developed a very poor dental arch relationship.

Maxillary arch dimensions were measured on the maxillary arch casts (1) intercanine distance = distance between the canine mesiobuccal cusp tips, (2) intermolar distance = distance between the second molar mesiobuccal cusp tips, and (3) maxillary length = distance in the midline from a point between the incisors to the posterior border of the maxilla. The intercanine distance was 27,64±1.57, the intermolar distance was 35.32±1.32 and the maxillary length was 29.63±2.14 in the two-flap group. In the one-flap group the intercanine distance was 27.32±1.87, the intermolar distance was 35.92±1.21 and the maxillary length was 30.02±2.04. This difference between the groups were not significant.

Level of evidence of the literature
The level of evidence regarding the outcome maxillary and midface growth started at high as it was based on a randomized controlled trial. The level of evidence was downgraded by two levels due to risk of bias (-1, incomplete accounting of patients loss to follow up) and due to the small study population (-1, imprecision).

2.5 Outcome measure postoperative complications (important)
Rossell-Perry (2017) reported an equal number of postoperative palatal fistulas in both the two-flap and one- flap group (n = 2; 2.85%). All fistulas were asymptomatic and located in the middle third of the palate.

Level of evidence of the literature
The level of evidence regarding the outcome postoperative complications was not graded due to the small number of events.

3. Lip closure
3.1 Outcome measure speech (important), 3.2 Outcome feeding capability (important), 3.3 Outcome measure maxillary and midface growth (important), 3.4 Outcome measure postoperative complications (critical)
These outcome measures were not reported in the included studies.

Level of evidence of the literature
The level of evidence regarding the outcome measures speech, hearing, and feeding capability, maxillary and midface growth, and postoperative complications were not assessed due to lack of studies.

3.5 Outcome measure esthetics (critical)

Three studies (Chowdri (1990); de Silva Amaratunga (2004); Williams (2011)) assessed esthetics. Due to heterogeneity of the different techniques evaluated in the studies, it was not possible to pool the data.

Chowdri (1990) report that the esthetic scores were similar in the patients treated with rotation advancement repair (71 ± 10) and triangular flap repair (73 ± 12, p> 0.50). There was also no significant difference for the lip scores alone (p>0.10) or the nose scores alone (p>0.80) between the two surgical techniques. Regarding postoperative complications, this study reports that 5/58 (9%) of the patients in the rotation flap advancement group developed scar hypertrophy compared to 2/50 (4%) in the triangular flap group (p>0.10). Furthermore, 4 patients in the rotation advancement group developed wound dehiscence, compared to 0 patients in the triangular flap group (p-value not reported).

De Silva Amaratunga (2004) reports that the Cleft Lip Component Symmetry Index score of philtral height, vermillion height, and Cupid's bow height achieved with the combined method was comparable to that achieved with Cronin's method and was superior to that obtained with Millard's method (p< 0.01). Further, the combined method achieved a Cleft Lip Component Symmetry Index score for the philtral width that was not significantly different from that of Millard's method and better than that of Cronin's method (p< 0.01).

In Williams (2011) only fistula rates were compared and were found not to be different between the Spina and Millard repair techniques. The esthetic result of the different lip-closure techniques was not compared in this study.

Level of evidence of the literature

The level of evidence regarding the outcome esthetics started at high as it was based on randomized controlled trials. The level of evidence was downgraded by three levels due to due to risk of bias (-1, incomplete accounting of patients loss to follow up) and limited number of included patients (-2, imprecision).

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of different techniques of repairing cleft lip, alveolus and/or palate on speech, hearing, feeding capability, maxillary and midface growth, postoperative complications and esthetics (patient, parent and/or doctor satisfaction)?

P: Patients with cleft lip, alveolus and/or palate
I: survival intervention with a specific technique for repairing cleft lip, alveolus and/or palate
C: survival intervention with another surgical technique for repairing cleft lip, alveolus and/or palate
O: Speech, hearing, feeding capability, maxillary and midface growth, postoperative complications, aesthetics (patient, parent and/or doctor satisfaction).

Relevant outcome measures

For cleft palate repair, the working group considered the following outcome measures as critical for decision making: Speech, hearing and feeding capability. Maxillary and midface growth, postoperative complications, and esthetics were considered as important.

For cleft lip repair, the working group considered the following outcome measures as critical for decision making: Postoperative complications, and esthetics were selected as critical.
Speech, feeding capability, and maxillary and midface growth, were considered as important.

Studies should report at least one of the outcomes of interest: Esthetics (patient, parent and/or doctor satisfaction), speech, feeding capability, postoperative complications. For the outcome speech, a follow-up until at least the age of four years. A follow-up length of at least one year was deemed sufficient for the outcome hearing. When papers reported a shorter follow-up time they were excluded.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinical (patient) important difference for the dichotomous outcome measures; RR < 0.80 or > 1.25)

No a priori criteria were set for the continuous outcome measures because it largely depends on its context. If no information was available about the clinically important difference of the outcome measure, a difference of ten percent between the groups was defined as a minimally clinically important difference.

Search and select (Methods)
A systematic search had been performed for the 2018 edition of the guideline in the databases Medline (through OVID), Embase and the Cochrane Library on December 3rd, 2014. This search identified 519 references, and 39 references were selected after reviewing title and abstracts. After checking eligibility of full text articles, 25 studies were excluded and 14 studies were included in the summary of literature, of which seven RCTs, and seven observational studies. To update the previous search, the databases Medline (via OVID) and Embase (via Embase.com) were searched with previous search terms until January 1st, 2020. The detailed search strategy is depicted under the Tab Methods. The systematic literature search resulted in 529 new hits. Studies were selected based on the following criteria: Studies including patients with were selected if they compared two different operative techniques in terms of closure of the soft palate. A total 14 studies (8 reviews and 6 RCTs) were initially selected based on title and abstract screening. After reading the full text, the 8 review studies and 4 RCTs were excluded (see the table with reasons for exclusion under the tab Methods), and 2 RCTs were included and added to the six RCTs of the previous search who met the selection criteria above.

Results
Two studies were added to the 2018 version of the analysis of the literature describing (lip and) palate closure; one study described the closure of palatum molle/soft palate and one study described the closure of palatum durum/hard palate. No studies describing lip closure were added. To distinguish between lip and palate closure and between hard and soft palate, the literature analyzes is divided in three parts:

1. Palatum molle / soft palate
2. Palatum durum / hard palate
3. Lip closure

Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Hearing problems in patients with a CLA/P

Primary question

What considerations (advantages and disadvantages) play a role in the treatment of hearing loss in children with a (cheilognatho) palatoCLA/P?

Recommendation

For each child with (cheilognatho) palatoCLA/P, request the results of neonatal hearing screening.

Carefully check the hearing of children with a (cheilognatho) palatoCLA/P. It is proposed that periodic examinations be carried out in an audiology center up to the age of 3-4 years and then as indicated by the ENT. It is recommended that these tests are aligned with the surgical protocol.

Check hearing in children with a (cheilognatho) palatoCLA/P at least once post-operative after insertion of eardrum tubes to rule out perceptive hearing losses (see Otitis media with effusion NVENT Directive, 2012).

Place eardrum tubes in children with a (cheilognatho) palatoCLA/P only as indicated (see Otitis media with effusion Directive), taking into account audiology findings and speech test results (and not only for the presence or absence of otitis media with effusion).

Considerations

Children with a (cheilognatho) palatoCLA/P are more likely to fail in neonatal hearing screening than children without a CLA/P. On the one hand, this is due to the frequent occurrence of otitis media with effusion, and on the other hand, due to the increased risk of permanent perceptive hearing losses due to syndromes. Because of this, neonatal hearing screening for children with CLA/P has been changed from 2 x OTO acoustic emissions (OAE) screening and then in 3rd instance Automatic Auditory Brainstem Responsions (AABR) for children without CLA/P to 1 times OAE screening and then in 2nd instance the AABR. With this, it is important to remember that the threshold of the OAE screening is 20-25dB and the threshold of the AABR screening is 40dB.

It is assumed that mild hearing losses of up to 35dB in otherwise healthy children generally do not lead to a delayed speech development in the first year of life. Furthermore, to date, it has never been conclusively proven that (recurrent) otitis media with effusion (the most frequent cause of mild hearing loss in the Netherlands) has a negative effect on speech development in otherwise healthy children.

On the other hand, in children with delayed speech development, hearing loss is often identified as a contributing cause. In view of these findings, there is an extensive discussion on the placement of eardrum tubes. In children with a CLA/P, this discussion is even more pronounced because of the anatomical abnormalities that are also present, which can also negatively affect the normal speech and language development. In some CLA/P teams, therefore, it is standard practice to place eardrum tubes at the

first surgery and any otitis media observed with effusion, while other CLA/P teams use tympanic membrane tubes only selectively. There are also large differences in the frequency of placement of eardrum tubes during further treatment of the CLA/P. However, there is now increasing evidence that this may lead to longterm negative sequelae with respect to ear and hearing status, without showing a significant difference in results between frequent placement of eardrum tubes and a more conservative approach.

Therefore, close cooperation with an audio-visual center could be considered, where an age appropriate auditory diagnosis can be performed particularly early in life and should be taken into account in the (indication of) treatment for middle ear problems. From 4 to 5 years of age, an audiological diagnosis can also be performed with sufficient confidence in the ENT. It may be proposed to treat otitis-based conductive hearing losses with effusion greater than 25-30dB. It would be possible to speed up treatment of delayed speech and language development.

In addition, since there is also a higher risk of perceptive hearing loss in the context of an unrecognized syndrome, close cooperation between ENT, audiological center and clinical geneticist is strongly recommended in the field of audiological and genetic diagnosis.

Substantiation Background

Hearing problems are common in children with (cheilognatho) palatoCLA/P. This usually involves otitis media with effusion due to the impaired function of the Eustachian tube based on reduced action of the velary musculature due to the CLA/P. In addition, permanent conductive hearing losses can occur due to congenital abnormalities of the auditory chain. Most of the time, this involves unrecognized syndromal forms of CLA/P. The same applies to perceptive hearing losses. These are also more common in syndromal forms of CLA/P. However, there are many syndromal forms of CLA/P that are not always recognizable immediately after birth. To date, there is no unanimity on the best moment and the best way of treating these hearing losses.

Conclusions

Very low GRADE	There is very little proof that VTI (ventilationtube insertion) may improve hearing outcomes in the children with cleft palate in the long run. *Kuo, 2014*

Very low GRADE	There is very little proof that early routine VTI may benefit children with cleft palate in the development of speech and language. *Kuo, 2014; Ponduri, 2009*

High	Ductive hearing impairment caused by otitis media with effusion is almost ubiquitous in children with C(L)P.

Moderate	Hearing results of early routine insertion of grommets are not different than in a conservative treatment with grommets.

Low	There seems to be a correlation between the frequency of grommet insertion and the long-term sequelae

Low	There is no difference in audiological results between treatment of HI due to persistent otitis by grommets or by hearing equipment.

Low	Treatment of otitis media with effusion by grommets results in more long-term sequelae than treatment by hearing equipment.

Low	Permanent hearing impairment (conductive and/or sensorineural) is more prevalent in children with than without C(L)P.

Summary of literature

Two systematic reviews by Kuo (2014) and Ponduri (2009) were included. Kuo (2014) studied the effectiveness of ventilationtube insertion (VTI) for OME in children with cleft palate. Kuo (2014) found in a systematic review (9 publications in which Gani, 2012; Kobayashi, 2012; Shaw, 2003; and Maheswar, 2002) evidence for a faster solution of hearing impairment by grommets than with conservative treatment in two studies, but not in three other studies. In one study (Hubbard, 1985) also positive long-term effects on speech development are found, but this could not be statistically confirmed in two other studies (Kobayashi, 2012; Shaw, 2003). Almost all studies report on more frequent otologic complications in children with than without grommets. Kuo concluded that all nine studies included in the review were observational cohort studies, which were initially graded as low-quality evidence according to the GRADE approach. For each outcome the studies (outcomes related to hearing, speech and language development, frequency of treatment, and complications or sequelae) were unable to adequate control for known confounding factors. Although the results of this study are evidence based, the studies included in the analysis are underpowered cohort studies, and the evidence for each outcome is of very low strength.

Ponduri(2009) performed a systematic review of randomized controlled trials, controlled clinical trials, case series, and prospective and historical cohort studies to determine whether early routine grommet insertion in children with cleft palate has a beneficial effect on speech and language development hearing with conservative management. They found many confusing and contradictory results in these studies concerning early routine grommet insertion versus grommet insertion in selected cases. Most studies were either small or poor quality or both. However, they concluded that there was insufficient evidence on which to base the clinical practice of early routine grommet placement in children with cleft palate.

In order to detect sensorineural hearing impairment (SNHI) earlier than before, neonatal hearing screening by Otoacoustic emissions (OAEs) and automated auditory brainstem responses (AABR) is introduced in the Netherlands since 2007-2008 (Ploeg, 2014). After detection at a very young age, HI can be diagnosed at Speech and Hearing CentrEs (6-8 weeks) (Guideline Dutch Federaton of Audiological CentrEs, 2014). SNHI will be treated by hearing equipment, while conductive hearing impairment can be treated by grommets immediately or by temporary hearing equipment until surgery is more convenient. Since otitis media with effusion often is temporary, also a wait-and-see policy is possible. Because there is still no scientifically proven deleterious effect of temporary conductive HI on speech language development in otherwise healthy children (Roovers, 2000), one can also choose to treat depending the speech development. By now, it is clear that grommets are the first choice of treatment when the otitis media with effusion is persistent (Dutch ENT Guideline for persistent otitis media with effusion 2012).

In children with cleft (lip) palate C(L)P otitis media with effusion is especially prevalent between 2 and 6 years of age and gradually diminishes between 7 and 13 years (Sheahan, 2003; Kuo, 2013). With or without otitis with effusion, hearing is often quite normal. Audiological research in non-cleft children proved an often only mild conductive HI in otitis media with effusion (Anteunis and Engel, 2000).

There is a debate whether the grommets should be placed routinely (often already during first surgery at the age of a few months) (Valtonen, 2005; Klockars, 2012; Merrick, 2007), or only in selected cases depending on the severity of the HI (Andrews, 2004; Kobayashi, 2012). There is no scientifically demonstrated difference between these two treatment options in outcome results with respect to hearing (Kuo, 2013; Tuncbilek, 2002; Phua, 2009) and speech language development (Kobayashi, 2012) in the long run. Even with a conservative treatment policy 28 till 98% (Shaw, 2003; Szabo, 2010) of the children are treated with grommets.

Because the otitis media with effusion often recurs soon after extrusion of the grommets, the effect of grommets seems only symptomatic and not causal (Broen, 1995; Kuo, 2013; Sheahan, 2003).

From the literature it is seems clear that there are negative long-term deleterious effects (tympanosclerosis, atelectasis, fixation of the middle ear ossicles, eardrum perforations) when grommets are inserted often (Phua,2009; Kuo, 2013; Kuo, 2015). There seems to be a relation with the number of insertions Especially T- tubes are notorious for persistent eardrum perforations after extrusion (Hornigold, 2008). Cholesteatoma can be seen in 1.5 – 6.9% of children with C(L)P (Spilsbury, 2013) and in 8 – 13% reconstructive middle ear surgery is indicated (Sheahan, 2003; Goudy, 2006).

With respect to the relation between type of cleft surgery and hearing and ear results, the conclusions are not clear; in a systematic review, Antonelli (2001) cannot demonstrate a difference in hearing results after palate surgery between the techniques of Furlow and von Langenbeck, while Carroll (2013) finds a small positive correlation in ear results after palate surgery with the Furlow technique versus the von Langenbeck and the Wardill-Killner techniques, respectively. However, after the age of 6 years this difference was not present anymore.

18-28% of children with C(L)P do not pass the neonatal hearing screening (CHEN, 2008; Andrews, 2004; Szabo, 2010). In most cases, there is otitis media with effusion, but one should be cautious for permanent

SNHI, often part of a syndrome that is frequently not clearly visible. Syndromes are present in 30-50% in cleft palate (Andrews, 2004) and in 14% in CLP. The chance of a permanent HI in C(L)P children who fail the neonatal hearing screening is estimated to be 5.4 times higher than in children without cleft (Chen, 2008). It is suggested therefore to first insert grommets after failing the neonatal hearing screening in cleft children in order to improve the audiological investigations and detect SNHI earlier (Jordan, 2014).

Hearing equipment

Instead of grommets, hearing equipment can be suggested as an alternative. The audiological results are comparable with those of grommets, but there are less complications and less long-term negative sequelae (Maheshwar, 2002; Gani, 2012). However, hearing equipment as an alternative is not often suggested to the parents (Tierney, 2013). A model-based cost-effectiveness analysis showed that grommets are the most cost- effective on the long term, followed by hearing equipment and that a wait and see policy is the least cost- effective (Mohiuddin, 2014).

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out about the following scientific question(s):

· What are the (dis) advantages of early placement of eardrum tubes compared to a wait-and-see policy in children with a (cheilognatho)palatoCLA/P or alternative forms of treatment?

The initial question has been translated into a scientific query. The working group is aware that this query can only answer part of the initial question.

P: Children with a (cheilognatho) palatoCLA/P;

I: Early standard treatment of hearing loss by eardrum tubes immediately at first CLA/P surgery at a few months of age and thereafter routine placement of eardrum tubes with each effusion otitis media;

C: Later initiation of treatment or alternative forms of treatment and selective placement of eardrum tubes;

O: Longterm results regarding hearing, ear status, speech.

Relevant outcome measurements

The workgroup considered hearing and normal eardrum and middle ear status to be an important outcome measure for decision-making, as well as a high degree of intelligible normal speech.

The working group did not define the aforementioned outcome measures a priori, but used the definitions used in the studies. With respect to hearing, normal hearing with a hearing threshold of better than 20dB was considered clinically relevant.

Search and study selection (methods)

A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 2000 and March 12, 2014. This search was aimed to identify systematic reviews, RCTs, ccts, and observational studies. Detailed search characteristics are shown in appendix X..

The initial search identified 109 references of which 15 reviews / RCTs and 94 other studies. After studying the abstracts, 28 were assessed on full text.. Two systematic reviews were found to be relevant for answering the above stated review question. 25 studies (9/15 reviews/RCTs and 19/94 other studies) seemed to be relevant for answering the other aspects of the clinical question on hearing loss, but not eligible for GRADE assessment. Furthermore, some national established guidelines (CBO, FENAC, ENT) were used. The evidence tables and risk of bias assessment are added as an appendix.

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Hypernasality in patients with a schizis

This module is divided into the following sub-modules:

- Diagnosis of hypernasality in CLA/P Treatment of
- hypernasality in CLA/P

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Diagnosis of hypernasality in patients with a CLA/P

Primary question

What is the best diagnostic strategy for the determination and analysis of velopharyngeal insufficiency (VPI) in children with a (cheilo-gnatho) palatoCLA/P?

Recommendation

Diagnose envelopharyngeal insufficiency multidisciplinary (at least surgeon, ENT and logopedist).

Only after a six-month period of specialized logopedics with insufficient treatment outcome should the diagnosis be made of envelope haryngeal insufficiency after primary palate closure, provided that a sufficiently long and mobile palatum molle appears to be present (at intra-oral inspection) and the child has been sufficiently instructable.

Have a logopedist participating in the national NVSCA working group for schislogopedists conduct the logopedic examination (Meijer, 2003) for the diagnosis of velopharyngeal insufficiency.

For the most complete imaging possible, preferably perform oral inspection, acoustic nasometry, mirror tests and nasendoscopy for the diagnosis of velopharyngeal insufficiency.

Perform a nasendoscopy if the child is likely to succeed (usually from three and a half years).

Perform video fluoroscopy as an alternative to diagnosing velopharyngeal insufficiency (for example, if nasendoscopy fails) or as an additional diagnostic for more information on field function.

It is preferable that the logopedist be present in nasendoscopy and video fluoroscopy. Take a photo or video of the

nasendoscopy.

After one year of speech enhancing surgery, repeat all pre-operative examinations, except for nasendoscopy/video fluoroscopy where appropriate, so that the effect of speech enhancing surgery can be determined as objectively as possible.

Repeat nasendoscopy/video fluoroscopy one year after speech-enhancing surgery if, at 6 months, specialized logopedics from the studies have shown signs of velopharyngeal insufficiency with insufficient intelligibility.

Do not perform MRI as a standard part of the diagnosis for the determination of velopharyngeal insufficiency.

Considerations

The most reliable diagnostic strategy for the determination of velopharyngeal insufficiency (VPI) remains unclear due to a lack of scientific studies that reliably compare the different diagnostic strategies. This way, the working group intends to present a proposal for a diagnostic strategy in the following section on which there is consensus within the working group. The minimum studies required to reliably determine the diagnosis of the velopharyngeal insufficiency are described. It also describes the minimum disciplines that should be involved in the diagnosis of VPI and at which points this diagnostic strategy can be applied throughout the treatment course. Finally, a flow diagram has been drawn up for clarification.

If there is a suspicion of the existence of VPI in a child with a CLA/P, a logopedic examination shall first be carried out by a logopedist from a CLA/P team, preferably in combination with oral inspection to rule out serious defects or a severely too short velum and to obtain a first impression of the mobility of the velum.

The logopedist makes an initial measurement of the speech, resonance and intelligibility of the child at the first appointment. If, after this study, the logopedist suspects VPI and the child is sufficiently cooperative and instructive, logopedic therapy will be initiated. In some cases this is sufficient to achieve good speech, resonance and intelligibility.
If a period of six months of specialized logopedic therapy does not have sufficient effect on speech and resonance and a child could not be instructed sufficiently during the treatments, the child will be seen again for follow-up studies within the CLA/P team.

The purpose of these follow-up check-ups is to collect relevant information about the VPI of the relevant child with a CLA/P in such a way that, based on that information, the CLA/P team:
a) will be able to make a well-founded decision as to whether or not to advise a speech-enhancing intervention.
b) determine the most effective technical variation of the speech enhancing procedure.

The age at which the follow-up studies are initiated varies on average between 3½ and 5 years and depends on the intelligibility, cognitive level, language level and participation of the child. If the child is reported to the CLA/P team at a later age, during the first visit, in addition to logopedic studies, studies should be performed to exclude a too short palatum molle or submucous palate. As these children almost always meet the criterion of six months of specialized logopedic therapy with insufficient effect, the diagnostic strategy described here and the flowchart below are followed.

Available studies
The following studies for diagnosis and analysis of VPI are known and available in Dutch CLA/P care:

A: Logopedic examination by the team's logopedist

The purpose of the logopedic research is to map the intelligibility, the speech problems and the resonance (usually hypernasality) resulting from a possible VPI (Kummer, 2011). In 2003, the logopedic study of children born with a CLA/P was developed (Meijer, 2003). In the Netherlands, this study is only conducted by logopedists working within a CLA/P logopedists team and as such are part of the National CLA/P logopedists Working Group, affiliated with the Dutch Association for CLA/P and Craniofacial Abnormalities (NVSCA). Consensual training (twice a year) within this working group ensures the quality of the decrease in logopedic research. A study, funded by the Dutch Association of Plastic Surgery, is currently underway to validate this logopedic study. The logopedic research consists of assessing speech at the word- and spontaneous speaking level, assessing the resonance and the possible presence of grimaces and conducting mirror tests. The intelligibility is ultimately judged on a five-point scale. Research by Klinto (2011) shows that judging speech at word level most reliably reflects a child's best performance. For assessing ongoing speech, repeating sentences is a reliable research method for children with a CLA/P. In this study, 20 children with and 20 children without a CLA/P were studied at the age of five years.

B: Oral inspection

If there is evidence of VPI after logopedic examination, an oral inspection of the palate should be performed. Ideally, both studies should take place on the same day. If the child’s palatum molle has already been operated, the aim is to estimate the height and mobility of the palatum molle, the mobility of the velum, the position of the levator veli palatini musculus and the presence of adenoid and tonsils. The purpose of this is to check for the existence of a biphide uvula or other evidence of a submucous palate.

On the other hand, the aim is to inspect the palatum durum for the presence of a fistula. Or, if the durum palatum is not yet closed, the size of the opening. An opening in the durum palate may be a negatively influencing factor and in some cases the root cause of hypernasality.

If there is a fistula in the durum palatum, it is recommended that this be closed during (part of) the logopedic examination, nasometry and naso endoscopy so that the influence of the fistula on hypernasality can be objectified. The temporary closure can be done with, for example, wafer or edible paper.

C: Mirror test

The mirror test is part of the logopedic study for children with a CLA/P. (Meijer, 2003). The purpose of the mirror test is to detect nasal air loss on some standard items (papa, pipi, kaka, kiki, ffff, ssss, ie, oe and the phrase 'Piet sits on the sidewalk'). This includes items with denasal consonants and vowels. During rehearsal of these items, a mirror is held under the child's nose after the child has started, so that any air loss can be seen in the form of condensation on the mirror. The mirror is removed from under the nose before the end of the repeat sequence. This is because otherwise the expiration will be visible on the mirror and the measurement will not be reliable. If condensation is seen on the mirror on one or more items, this is an indication of the presence of VPI.

D: Acoustic nasometry

It is preferable that the logopedist, in addition to the logopedic examination, including the mirror tests, also performs acoustic nasometry. This is because it is an objective measurement (Karnell, 2011; Sweeney and Sell, 2008; Brunnegard and others) 2012). Standard texts are recommended (Van de Weijer and Slis, 1991; Van der Heijden, 2011). The standard texts and standards used in the Netherlands by the logopedists from the CLA/P teams are listed in the Annex.

The reliability of the measurement also depends on the co-operation (and age) of the child. The child should be able to reproduce the standard phrases and accept the helmet to be worn during nasometry. Research by Van der Heijden (2011) shows that the majority of children aged six years and older can cooperate with the acoustic nasometry. Children aged 6 years were significantly more cooperative than children under 6 years of age. For children aged four and five, the cooperation depends very much on the situation. In this study, 159 children between four and six years of age were studied.

In the Netherlands, not every CLA/P team has a nasometer at the moment. The teams that have a nasometer use different types of nasometers from the firm Kay Pentax. The different types of Kay Pentax brand nasometry values show only minor differences which are subjectively undetectable (Kay Pentax Instruction Manual Nasometer II, 2010). Thus, it is plausible that the values on the nasometry are similar between the Dutch CLA/P teams if the decrease in nasometry is similar in terms of procedure and expressions and it is a Kay Pentax nasometer. It is desirable that every CLA/P team has a nasometer, as this is one of the few objective measurements to determine a different resonance.

If VPI is diagnosed and a (surgical) treatment is followed, acoustic nasometry can be repeated before and after treatment. The interpretation of the nasometry values must take the child's speech pattern into account. If a child has compensatory speech for speech-enhancing surgery, this may have positively affected the nasometry values. Although the nasometry is an objective measurement, the data from the logopedic study should therefore always be taken into account in order to reliably assess the speech and resonance and the progress made on it.

E: Nasendoscopy

The plastic surgeon, ENT and/or logopedist performs the nasendoscopy (Karnell, 2011) with the aim of mapping the field function (levator veli palatini musculus), as well as the function of the surrounding muscles and the possible presence of a (substantial) adenoid to compensate for a possible VPI. The advice is to use standard versions (see appendix). Capturing the nasendoscopy on video is necessary for documentation, but above all for multidisciplinary discussion and interpretation of the images in the precision team.

The physician can use nasendoscopy to assess whether there is a non-functional closure between the nasopharynx and oropharynx during speech. If this is the case, it is VPI. Depending on the size of the opening, the action of the levator veli palatini musculus and the surrounding muscles

follow-up policies should be defined in a multidisciplinary context. Logopedic studies and nasendoscopy map the anatomical and functional basis of the child and these studies contribute to the decision-making for a speech-enhancing procedure (Rayan, 2014). The nasendoscopy gives a detailed picture of the anatomy of the pharynx, presence or absence of an adenoid, the dynamics of the levator veli palatini musculus and the surrounding muscles during speech, also reveals very small defects. In addition, the child is not exposed to radiation and the costs are low. However, there are also several drawbacks. The child's cooperation is required and the size of the opening cannot be reliably determined (Howard, 2011). However, it is not possible to reliably measure the size of the opening with images of the nasendoscopy, so it is not possible to make an objective comparison of the size of the opening before and after surgery. It is also possible that speech may be affected by a stimulation of the nasoendoscope in the nose or reduced sensory feedback if local anesthesia is used.
The chance of successful nasendoscopy depends on the doctor's experience and the cooperation of the child. It is therefore recommended that this study be carried out with two persons at all times and that an image and sound recording is made of the test. Practice has shown that nasendoscopy can be antagonistic for the child. It is therefore important to instruct the child and the parents in advance so that they come to the test sufficiently prepared. Usually a child from the age of three and a half to four years is sufficiently cooperative.

F: Video fluoroscopy

If the nasendoscopy is not successful or is not (yet) possible, video fluoroscopy can be performed as an alternative. A video fluoroscopy has the advantage that it is easy and fast to use and can be used in very young children. Using video fluoroscopy, the field function can be mapped from different angles (Karnell, 2011). This study also provides information on the possible non-functional closure between nasopharynx and oropharynx during speech and can be used as a pre- and post-ok measurement. However, there are also several drawbacks: it is a two-dimensional picture and the costs are high (Howard, 2011). The radiation required for this may also be seen as a disadvantage by the child's parents or guardians. The child's cooperation is also required in this test. The child must be able to imitate sounds, words and phrases. It is also very important that the child can sit still during the examination for optimal imaging. This can be facilitated by creating a head restraint, with eye protection built in. It is desirable that the logopedist be present during this examination.

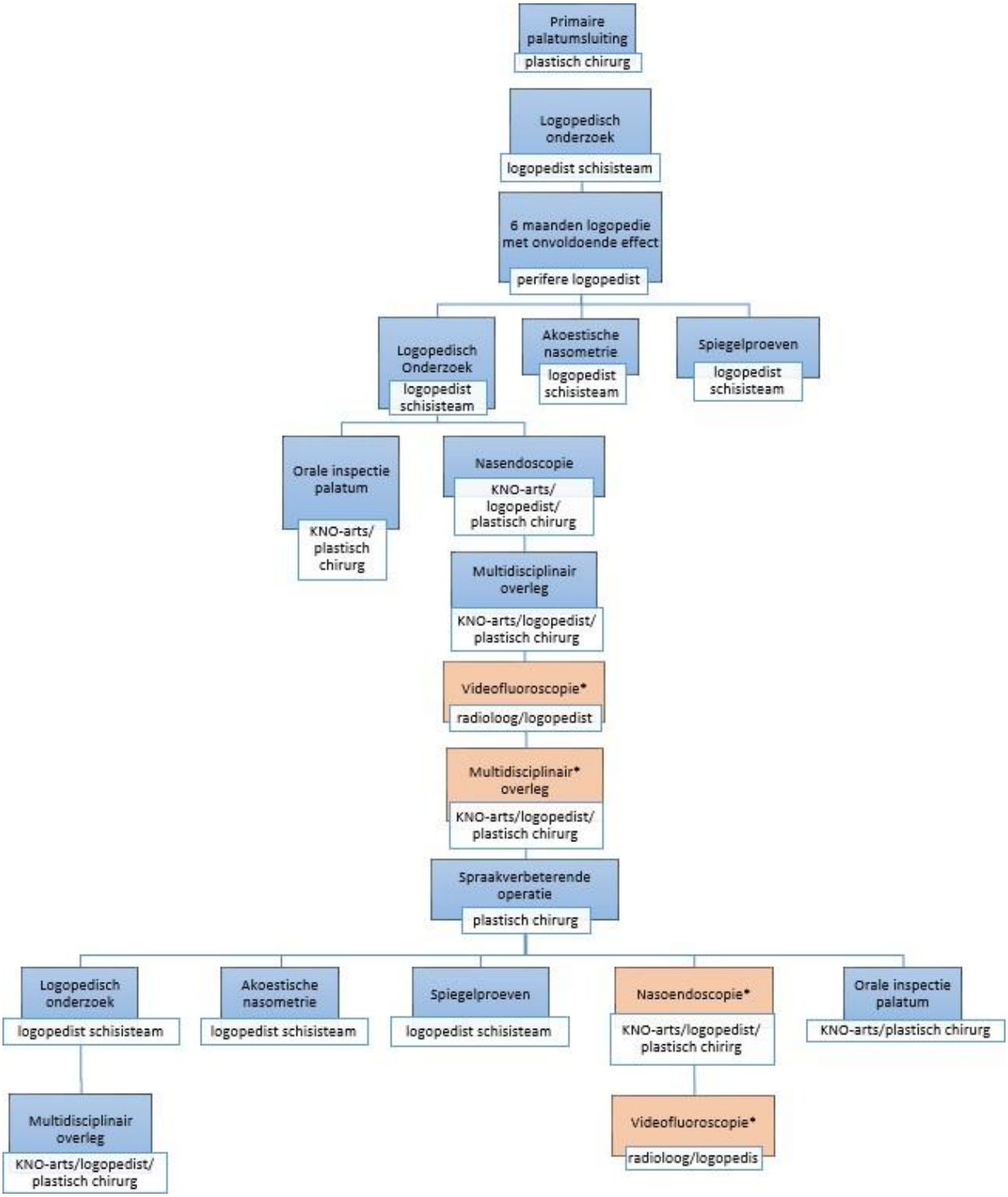
In general, the advice is to give both parents and the child good information and instruction on the conduct, course and purpose of a test.

G: Functional MRI

There are indications that functional MRI will in the future become a useful additional technique to diagnose VPI (Kuehn, 2001; Howard, 2011; Perry, 2014). Study protocols have already been developed for the use of MRI for the purpose of diagnosis of VPI. However, further research is needed to make this protocol applicable in daily clinical practice (Perry, 2014). The advantages of the MRI that are mentioned are: The reproducibility of the examination, it is a non-invasive examination, no ionic radiation is required and an MRI provides detailed information about the levator veli palatini musculus. The disadvantages are mentioned as high costs, long duration of the test and noise (Howard, 2011).

In the Netherlands, MRI is not used (yet) to diagnose VPI. This seems to be due, among other things, to the costs of the test.

Diagnostic Strategy Schematic View at VPI



* Optional tests/activities are shown in orange. If the nasendoscopy is not successful or is not (yet) possible, video fluoroscopy can be performed as an alternative.

Substantiation Background

In children with a (cheilo-gnatho) palatoCLA/P, speech and resonance problems may occur which do not fit in with normal speech development. These speech and resonance problems are usually caused by velopharyngeal insufficiency (VPI). VPI is defined as an inability of the velum and the lateral and posterior pharyngeal walls to separate the oral and nasal cavities while speaking and/or swallowing (Collins, 2012). VPI is a relatively common problem in children with a CLA/P of at least the palatum and may occur before and after the surgical correction of the palatum (Collins, 2012). This is usually caused by a too short or too little mobile palatum molle (velum), but can also be due to control problems or a combination of factors. Another possibility for the development of speech and resonance problems is the presence of a (residual) opening in the durum palatum.

As a result of VPI, children have difficulty controlling the airflow orally while speaking. Among other factors, this oral airflow is necessary for the correct realization of various speech sounds. As a result of VPI, hypernasality (on the vowels) and/or nasal snore (on the consonants) develop. Also, compensation strategies in speech can arise in the form of, for example, glottal realizations or glottal reinforcements, pharyngeal productions, backing and/or active nasal productions.

The diagnostic phase in which the voice and/or resonance problems and the (degree of) VPI are identified has a variety of available studies and there is considerable practical variation between the precision teams in this area. The following studies are used in the Netherlands: Logopedic research (including mirror tests), nasendoscopy, (acoustic) nasometry and videofluoroscopy. The diagnosis of hypernasality aims to identify which studies should be minimally performed to reliably diagnose VPI. Factors such as reliability, objectivity, burden on the child and cost-benefit play a role here. More uniformity in the diagnosis of VPI is desirable in order to obtain the best end result for the treatment and to be able to compare treatment results between the different CLA/P teams.

Conclusions

Not applicable.

Summary of literature

No relevant papers comparing two diagnostic methods for diagnosing velopharyngeal insufficiency (hypernasality) in children with cleft palate with a suspicion of speech impairment were found.

Search and select

In order to answer the initial question, a systematic literature analysis was carried out based on the following PICO:

P: non-syndromal (cheilo-gnatho) palatoschis patients with closed palatum and speech and

resonance problems (especially hypernasality, velopharyngeal insufficiency);
I: Diagnosis of velopharyngeal insufficiency by logopedic examination, nasometry, nasendoscopy, videofluoroscopy, MRI;
C: Comparison of diagnostic tools;
O: diagnosis of velopharyngeal insufficiency (VPI, hypernasality, gapsize).

Relevant outcome measurements
The working group defines the diagnosis of velopharyngeal insufficiency (hypernasality) as a critical outcome measure. VPI refers to a non-functional closure between the nasopharynx and oropharynx during speech, so that normal speech and/or resonance cannot follow.

Search and selection (Method)
Medline (OVID), Embase and the Cochrane Library were searched with relevant search terms between January 2007 and 27 November 2014. Reviews, RCTs and observational studies were included. The search strategy can be found in the appendix.

Studies were selected based on the following selection criteria: Clinical research comparing two diagnostic methods to diagnosis velopharyngeal insufficiency (hypernasality) in children with a cleft palate with a suspicion of speech impairment (specifically open nasality, velopharyngeal insufficiency).

A total of 245 papers were found with the literature search. Based on the title and abstract, 71 papers were selected. None were selected based on the full text (see the exclusion table in the appendix).

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For full reports, evidence tables and any related products, please refer to the Guideline database
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Treatment of hypernasality in patients with a CLA/P

Primary question

What is the best surgical treatment strategy if there is velopharyngeal insufficiency in children with a (cheilo-gnatho) palatoCLA/P?

Recommendation

Choose a specific surgical technique based on preoperative logopedic examination combined with a test such as nasendoscopy and/or video fluoroscopy (see Hypernasal Diagnostics module).

Consider intravelar palatum plastic with palatal muscle repositioning before proceeding to pharyngeal plastic in case of persistent velopharyngeal dysfunction despite previously closed palatum.

In the case of persistent velopharyngeal insufficiency despite the repositioning of palatal muscles, consider pharyngeal plasty based on re-diagnosis such as nasendoscopy and/or videofluoroscopy.

For submucous palatoCLA/P, consider single palatal plastic over combined surgery of palatal plastic with pharyngeal plastic.

Use fat injection only in the context of scientific research.

Considerations

The most optimal surgical method for correcting VPI remains controversial due to a lack of well-randomized controlled, prospective studies comparing different surgical techniques. In addition, the above and later studies lack adequate length in clinical follow-up (at least three years) to estimate the surgical outcome over time. Moreover, there is no consensus on the objective diagnostic means of making a good comparison of surgical techniques. An important part of the differential diagnosis of VPI, in a previously corrected palatum, will also have to include the possibility that the previously performed palatoplasty with intravelar veloplasty has not healed completely. After all, the recovered muscular sling may have become dehiscent or once again attached to the back of the palatum durum. An indication of this may be a complicated palatum healing or paralysis with reduced mobility. However, there is no research comparing a renewed intravelar veloplasty with other speech-enhancing operations.

In the view of the limited number of scientific studies, the working group would also like to add for consideration those comparative studies describing other surgical techniques or combined techniques.

Carlisle (2011) performed a retrospective analysis in 46 patients with CLA/P (palatum CLA/P no (80%) submucous CLA/P (20%, including velocardial facial syndrome) and VPI where sphincter pharyngoplasty (SP; n=20) was compared to sphincter pharyngoplasty combined with a Furlow platoplasty (SP+; n=26). An outcome measure of this study was the risk of revision surgery due to persistent hypernasality. The two groups were not comparable in indications and differed in such a way that the SP+ group consisted of patients with a greater distance from velum to pharyngeal posterior wall, recorded by nasendoscopy. The results of this study showed that in the SP group more revision surgery was required than in the SP+ group (25% vs 4%).

A retrospective comparative study by Meek (2003) describes a population of 93 patients with VPI, in which a caudal (n=53) or cranial (n=40) steeled pharyngeal posterior swab was performed. The choice of the stem was made perioperatively depending on the presence of enlarged adenoid and on the size of the distance from velum to posterior wall. From a logopedic point of view, all patients showed improvement in articulation, air loss, and hypernasality. The improvement in VPI was significantly greater if operated before the sixth year of life. No difference was shown between the two techniques. A major limitation of this study is the large difference in phenotyping that led to the VPI (group consisting of: Congenital short palatum, complete CGP CLA/P to submucous CLA/P).

Both studies indicate that the option chosen depends on the preoperative study and the preoperative findings of the velum, adenoids and the distance to the pharyngeal posterior wall. This way a good result can be achieved both with combined interventions and with caudal and cranial plasty.

Ysunza (2001) investigated 203 patients, eventually including 72 children with a non-syndromal submucous palatoCLA/P and VPI. All children were subjected to both oral and logopedic examinations, nasendoscopy and videofluoroscopy. 2 groups were randomized; a standard minimal incision palatopharyngoplasty (MIPP) was performed in the control group (n=37) and in the experimental group, MIPP was combined with individualized surgery based on preoperative diagnosis (n=35; 32 pharyngeal lap, 3 sphincterplasty). The same results were found in both techniques for complete closure (86% in group 1 versus 89% in group 2) and velopharyngeal distance. Sleep apnea was not detected in any of the patients after surgery. This is partly due to screening for enlarged tonsils which would otherwise have been surgically removed at the earliest opportunity before moving on to pharyngeal or palatal plasty. Given the minimal differences between the two surgical techniques, the authors' advice is to opt for the least invasive technique without additional pharynxplasty and to correct residual VPI at a second pace with a more individualized pharynxplasty.

The working group feels that the benefit of combined operations on the palatum and pharynx to correct VPI over a single procedure is not sufficiently proven. The recommendation is to separate the operations, and recommending that the first step must be to redo the palatum.

Keuning (2009) performed an observational longitudinal study in 130 patients with residual VPI after

prior surgery on the palatum involving a steel cranial posterior pharyngeal flap. The case-mix in this study was large consisting of partly unilateral cheilognathopalatoCLA/P, partly bilateral cheilognathopalatoCLA/P, partly submucous or isolated palataloCLA/P and also syndromal patients. 15% required surgical intervention and few complications occurred. Given that the authors had similar results with the steel cranial posterior pharyngeal flap in comparison to other techniques described earlier, they particularly emphasize the surgical sides of the technique. The working hypothesis is examined to establish whether an experienced surgeon will have fewer complications and thus a better functional result. The authors stress that the outcome of the intervention is often difficult to estimate due to, among other things, the concept of tube formation/shrinkage and shortening of the flap in the pharynx area. It is advised to cover the raw surface of the pharynx flap in order to reduce tubing (Keuning, 2009; Rintala and Haapanen, 1995).

The study showed that no distinction could be made based on the experience of the operators, since the youngest operator had less complications than the eldest. It is concluded that the individual technical skills of the surgeon are more important than the surgical experience to minimize complications.

Autologous fat injections (lipofilling)
A relatively new intervention to treat VPI is the autologous fat injection (lipofilling). During a systemic review (Bishop, 2014), the literature on posterior pharyngeal augmentation was systematically investigated; from artificial additives such as silicone and goretex to biological material such as cartilage and lipofilling. Eleven lipofilling studies were included, 3 of which described selective augmentation of the pharyngeal posterior wall and the other 8 studies described augmentation of palatum molle/pharyngeal bows and pharyngeal posterior wall. None of these 11 studies were comparative. No meta-analysis was possible due to the strong heterogeneity of the population. No comparable diagnostic resources were used nor were good comparative objective post-operative assessments provided. All studies used the same technique for obtaining the fat (Coleman set). The amount of remaining volume of injected fat in the short and longer term was not consistently reported, except as demonstrated in the study by Filip (2011) who found an association between the volume of fat injected on MRI and reduction of the velopharyngeal distance. However, no actual clinical change of the VPI was reported in this study.
A preferred site for injection of fat has not been demonstrated. Only 1 complication was reported,
this was an increase in fat with an increase in the weight of the child over a period of 31 months. This resulted in obstructive sleep apnea symptoms. The conclusion that the authors gave from this systematic review is that fat injection appears to be a simple, relatively inexpensive technique with few complications. However, there is important information missing about patient selection, volume and location of fat injection as part of the amount of resorption of the injected fat depot and the result in comparison to other existing surgical techniques.

The working group considers the use of lipofilling as yet unproven to be effective in treating VPI. The working group therefore considers that VPI correction by lipofilling should only be applied if no other surgical options are available.

General considerations

In the absence of a proven effective universal operative approach to VPI, the choice of a technique will have to rely on a good preoperative evaluation of the form of VPI, based on the study as described in the VPI diagnostic module. A report should be compiled about this preoperative and peroperative examination and should maybe be repeated post-operatively. This should not only be done to monitor the success or failure of the treatment, but also as a registration and possibility of comparison. The age at which a VPI correction operation can best be performed will need to be determined jointly by the practitioners, with guidance on instruction for logopedic exercises. This instruction can be tested during the logopedic speech test which should be included in the standard diagnostics prior to surgery.

Given the limited demonstrated differences between posterior pharyngeal augmentation and pharyngosphincter plasty, both techniques appear similar in terms of clinical efficacy.

One of the possible reasons for the limited differences between techniques could very well be caused by, among other things, the limited sample size of the different studies and the diversity of diseases of the patients included leading up to the VPI. In order to demonstrate a 20% difference between different techniques within a study with an expected 10% loss of the study population, a group size of 292 patients (Åbyholm, 2005) was calculated. In order to reach these numbers, a call is made to start as many identical studies as possible, knowing that the number of hospitalizations is low.

Substantiation Background

The purpose of surgical treatment of velopharyngeal insufficiency (VPI) is to restore a functional closure between nasopharynx and oropharynx so that normal articulation and speech can follow. Several procedures for the secondary treatment of velopharyngeal insufficiency have been described, where repositioning of the palate musculature to a more anatomical position (compound placed in the median and more to posterior) should be at the top, even if this procedure has already been performed before.

Additional techniques include posterior pharyngeal augmentation (cranial or caudal steel), sphincter pharyngoplasty (such as Orticochea), combination of palatum lengthening and cranial steel pharynxl flap (modified Honig), palatoplasty (Furlow Z plasty or uni/-bilateral Buccal flaps), and posterior pharyngeal augmentation (e.g. fat injection or Hynes). Each treatment option has advantages and disadvantages. The purpose of this baseline question is to determine the preferred surgical treatment strategy in the event of velopharyngeal insufficiency in a patient with a CLA/P where a primary palate closure has already been performed.

Conclusions

Very low GRADE	We found very little proof that pharyngeal flap and sphincter pharyngoplasty are equally effective in treating velopharyngeal insufficiency. *Ysunza, 2004; Åbyholm, 2005*

Very low GRADE	We found very little proof that pharyngeal flap and sphincter pharyngoplasty result in comparable complications in treating velopharyngeal insufficiency. *Ysunza, 2004; Åbyholm, 2005*

Summary of literature

Study characteristics

The study by Ysunza (2004) concerned a 7-year prospective study to assess the planning and results of pharyngeal flaps and sphincter pharyngoplasties for correcting velopharyngeal insufficiency. The customized pharyngeal flap and sphincter pharyngoplasty were performed according to findings of videonasopharyngoscopy and multiview videofluoroscopy. The study population consisted of 70 patients with complete unilateral cleft lip and palate with no other medical conditions, which was randomly divided into two groups. Palate repair was performed before 8 months of age in all patients. Age ranged from 4 years and one month to 7 years and 10 months (median: 5 years, 2 months) in the group with a pharyngeal flap, and from 4 years and 5 months to 7 years and 7 months (median: 5 years 4 months) in the group with sphincter pharyngoplasty. Outcomes were evaluated postoperatively and after four months. No loss to follow up was reported.

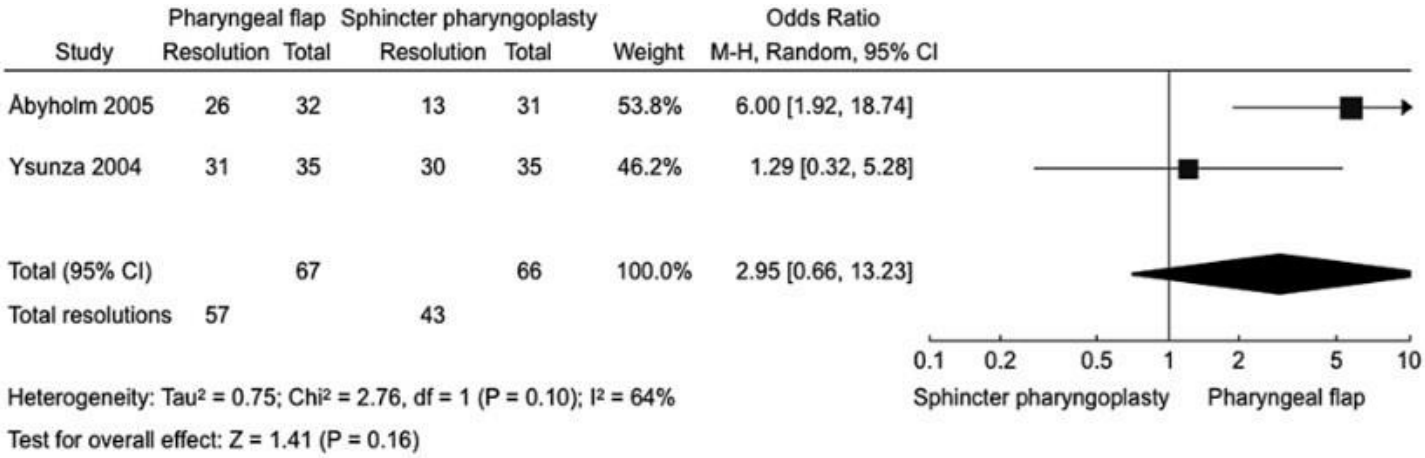
The study by Åbyholm (2005) is a randomized clinical trial comparing pharyngeal flap and sphincter pharyngoplasty for correcting velopharyngeal insufficiency in 97 patients with a repaired cleft palate with no other medical conditions were randomly divided in two groups. Patients, aged 3 to 25 years old, were evaluated at both three months and one year.

Results

VPI resolution

Whereas Ysunza (2004) reports no significant difference in VPI resolution between the groups, Åbyholm (2005) found a significant difference in favor of pharyngeal flap (P = 0,005). The pooled odds ratio for VPI resolution calculated by Collins (2012) was found to be 2.95 (95% CI: 0.66 - 13.23) in favor of the pharyngeal flap. In figure 2 the forest plot from Collins (2012) is shown. The meta-analysis by Collins (2012) included the selected studies by Ysunza (2004) and Åbyholm (2005). Collinset (2004) pooled the data of the two studies (133 patients) to calculate a pooled odds ratio for VPI resolution. This figure shows the number of patients with resolution of VPI after pharyngeal flap and sphincter pharyngoplasty procedures at follow-up times of 3 to 4 months for the RCTs of Åbyholm and Ysunza. Odds ratio and 95% confidence intervals for each study and for the meta-analysis as a whole are shown.

Figure 2. Pooled odds ratio for VPI resolution (Collins, 2012)



Although Åbyholm (2005) found a high level of clinical improvement for both surgical interventions, at 3 months postsurgery, elimination of hypernasality was found in twice as many patients after flap surgery (significant). At 12 months post-surgery, however, Åbyholm found no statistically significant difference in VPI resolutions between the sphincter and pharyngeal flaps procedures, resp. 78% vs. 83% (P = 0.45).

Postoperative complications

Both studies reported no differences in postoperative complications between the groups. Åbyholm reported low complication rate, low reoperation rate, and no significant differences between the two procedures. In addition, Åbyholm found that both procedures rarely resulted in clinically significant sleep apnea directly after surgery or on long-term incidence. This was assessed by carrying out overnight polysomnograms 1 month prior to surgery, and repeated 4 to 6 weeks and 1 year after surgery.

Grading the evidence

Grading the evidence started at the level of high evidence. Downgrading with three levels was, however, necessary as the sample size needed for statistical significance was not achieved, and due to heterogeneity of results. The number of patients, and for some outcomes like complications the number of events was very low.

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out on the following scientific question:

P: Non-syndromal (cheilo-gnatho-palato)CLA/P patients with closed palatum with velopharyngeal insufficiency;
I: Pharyngoplasty; palatoplasty; posterior pharyngeal augmentation; fat injection therapy;
C: Comparison of surgical options;
O: Speech; presence of (open) nasality (gap size); revision surgery; and postoperative complications or adverse reactions (sleep apnea, dehiscence/lesion of flap).

Relevant outcome measurements

The working group did not define the outcome measurements a priori, but used the definitions used in the

study. The working group considered the success rate of the procedure (defined as postoperative (open) nasality) a critical outcome measure for decision-making, and speech and complications or side effects for decision-making important outcome measures.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and April 9, 2014. This search was aimed to identify systematic reviews, RCTs, controlled clinical trials, and observational studies. Detailed search characteristics are shown in the appendix.

Studies that included patients with repaired cleft lip and palate were selected if they compared surgical interventions to correct velopharyngeal insufficiency. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: Speech, hypernasality, hyponasality, adverse effects and/or complications.

Results selection
The initial search identified 315 references. After selection 11 studies were found describing VPI and assessed full-text Nine studies were excluded because these studies did not meet the inclusion criteria (see appendix). One of these 9 studies was a systematic review/ meta analysis (Collins, 2012). However, in addition to this review two RCT studies were described which do meet the inclusion criteria. The evidence table and risk of bias assessment table are added as an appendix.

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Bone grafting procedure in patients with a CLA/P

This module is divided into the following sub-modules:

- Timing of bone grafting procedure in CLA/P
- Technique bone grafting procedure in CLA/P

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Timing of bone grafting procedure in patients with a CLA/P

Primary question

What considerations (advantages and disadvantages) play a role in determining the moment (timing) of bone grafting surgery in a patient with uni- or bilateral cheilognatho (palato) CLA/P?

Recommendation

Preferably close the cleft jaw using an early secondary bone grafting procedure.

Base the time for bone grafting procedure on the position and stage of root formation (½ - 2/3) of the cuspidate on the CLA/P side. The presence of a lateral incision and the moment of its breakthrough may advance the time. As indicated, the position of the central incision may be important.

Choose the time of the bone grafting surgery in close consultation with the treating orthodontist.

Consider the tertiary bone grafting procedure only in cases where no (secondary) bone grafting took place or then there is not enough bone present in the gnathoCLA/P, for example, for an implant at a later age. Tertiary bone grafting can also occur in adult age.

Considerations

The application of a bone graft into the jaw cleft in patients with uni – or bilateral cheilognathopalatoCLA/P is a permanent part of the treatment of this patient group. Regarding the timing of this procedure, there is a preference in the literature for the early secondary bone grafting (BIG) procedure, so before the cuspidate on the CLA/P side has broken through into the cleft. In the Netherlands, this is also the most popular time for this procedure. It seems there is little space in the Netherlands for primary and tertiary BIG treatment and also based on the literature consulted, the timing of treatment is further disregarded. An exception to this is those cases where, for some reason, there has been no BIG procedure in childhood and a BIG procedure can still be done at an older age. Strictly speaking, this is a tertiary BIG.

Based on the literature consulted, there does not seem to be a hard burden of proof for the choice between an early or late secondary BIG procedure. In the literature studied, the overall success rate, thus cumulatively measured across several outcome parameters, of early secondary BIG is higher. Despite the many variables, this appears to be particularly true for the important outcome measures, eruption of the cuspidate and/or lateral incision in the transplanted bone in the crevice and residual bone height/bone volume remaining after the procedure. The important reason for this is that the erupting cuspidate has a beneficial effect on the build-up and maintenance of the transplanted bone. This appears to be an essential factor to prevent resorption and to maintain accumulated bone levels during healing.

The higher overall success rate for early secondary BIG applies to both the uni- and the

bilateral cheilognathopalatoCLA/P. However, the literature shows that this success rate is generally lower in bilateral CLA/P than in unilateral CLA/P. The reasons mentioned above include the fact that bilateral cheilognathopalatoCLA/P involves a larger defect (and a greater shortage of soft tissue), a lesser vascularization and more scarring. This makes it more difficult to obtain a good closure over the transplanted bone.
In the literature, no further complications at the other times of closure are generally described compared to the early secondary closure. However, there is very little burden of proof for this.

Bone graft timing should be closely coordinated with the treating orthodontist. The degree of eruption and the stage of root formation of the angular tooth on the crevice side play a role in this. If the lateral incision is present, has a normal shape and root formation and threatens to break into the gap this may be a reason to advance the BIG. A single study recommends the BIG procedure even before the central and lateral incision have broken through to improve the retention and gingival condition of these elements and prevent them from migrating into the gap. In this context, the patient may sometimes have the desire to correct an aesthetic disturbing rotated central incision, but this can only be done after the BIG procedure. This may be a trade-off to advance the time when the BIG procedure will be performed.
The literature consulted did not disclose much about the effect of timing on maxilla growth. In a cephalometric study, Semb (1988) studied the growth of the upper jaw in patients with a single-sided CLA/P who received their bone graft before their 12th birthday in comparison to a group who did not have a bone graft (historical control group). She felt that a bone graft at 8-9 years of age had no effect on the forward and vertical growth of the maxilla. At this age, the forward-backward and transverse growth of the front part of the maxilla is already mostly complete, only the vertical one is not yet. The effect of surgical intervention on the growth of the maxilla is therefore very limited at this age.

Substantiation Background

In patients with cheilognatho (palato) CLA/P, a bone graft is applied to the jaw at a given time and any existing oronasal communication is closed. A bone bridge is made created both jaw segments, these are stabilized and the base of the ala nasi on the CLA/P side is thus supported. It also allows the cuspidate and/ or lateral incision on the CLA/P side to erupt. Timing and technique of this procedure are important.

In terms of timing, in the Netherlands, an early secondary closure is usually chosen, i.e. when the root of the cuspidate is formed ½ to ⅔ and before it breaks into the gap. In practice, that means between 9-12 years. If the procedure is adapted to the breakthrough of the lateral incision, the procedure can sometimes take place as early as the eighth year of life. Other less common times for gnathoCLA/P closure and bone graft application are: primary closure/bone graft at the closure of the lip and/or palatum molle (primary bone graft) and leave secondary closure if the cuspidate on the CLA/P side already broke through. Tertiary closure of the cleft occurs at adult age.

Conclusions

Early secondary vs.late secondary bone grafting

Very low GRADE	We found very little proof that in cases of unilateral cleft lip, alveolus and palate, early secondary bone grafting is more effective to facilitate eruption of the canine at the cleft side compared to late secondary bone grafting. *Nishihara, 2014*

Very low GRADE	We found very little proof that early secondary bone grafting is more effective to provide adequate alveolar bone height. between the nasal floor and the alveolar crest compared to late secondary bone grafting. *Rawashdeh, 2007; Freihofer, 1993; Sindet-Pedersen,*

Very low GRADE	We found very little proof that early secondary bone grafting has better results to facilitate an acceptable bone bridge compared to late secondary bone grafting. *Nishihara, 2014*

Very low GRADE	We found very little proof that early secondary bone grafting causes fewer fistulas and other complications compared to late secondary bone grafting. *Miller, 2010; Jia, 2006; Sindet-Pedersen,*

Very low GRADE	We found very little proof that early secondary bone grafting has better results on septal heights compared to late secondary bone grafting for uni- and bilateral cleft lip patients. *Jia, 2006*

Very low GRADE	We found very little proof that the success rate of early secondary alveolar bone grafting, in unilateral cases, is better (90%) than in late secondary alveolar bone grafting (SABG) (80%). The success rate of unilateral SABG is better than in bilateral SABG. *Rawashdeh, 2007; Freihofer, 1993*

Early secondary vs.tertiary bone grafting

Very low GRADE	We found very little proof that secondary bone grafting has better results on septal heights compared to tertiary bone grafting, in unilateral cleft and palate patients. *Trindade-Suedam, 2012*

Very low GRADE	We found very little proof that early secondary bone grafting is more effective to facilitate bone volume between the nasal floor and the alveolar crest compared to tertiary bone grafting. *Dempf, 2002; Freihofer, 1993*

Very low GRADE	We found very little proof that early secondary bone grafting causes fewer fistulas and other complications compared to tertiary bone grafting. *Dempf, 2002*

Summary of literature

Study characteristics

Out of eight included studies, six studies compared early secondary bone grafting to late secondary bone grafting prospectively (Rawashdeh, 2007) or retrospectively (Freihofer et al, 1993; JIA, 2006; Miller, 2010; Nishihara at Al, 2014; Sindet-Pedersen, 1985). For these studies, sample sizes ranged from 21 to 313 participants. Nishihara (2014) limited the inclusion to patients with a unilateral cleft. Miller (2010) compared bone grafting before and after eruption of the central incisor. This study and the other studies included patients with unilateral and bilateral clefts.

Two of the included studies compared secondary with tertiary bone grafting (Dempf et al, 2002, Trindade et al, 2012). Dempf at Al (2002) performed a retrospective study comparing early secondary bonegrafting with bone from the iliac crest during the mixed dentition period (mean age 10.6 yrs) with tertiairy bonegrafting (mean age 21.3 yrs) in a mixed group of unilateral and bilateral clefts. The length of follow-up is not stated. Trinsdade-Suedam et al (2012) did a prospective study (n=52) in which they compared two groups of patients with alveolar bone grafting using iliac crest bone with a unilateral cleft lip and palate after 2 and after 6-12 months. Group A received secondary bonegrafting during the mixed dentition period before or after eruption of the permanent canine (age 10-13 years), group B had their bone grafting procedure in the permanent dentition (age 15-28 years). Both studies had a significant number of drop-outs (37.0 and 39.3%).

All treatments were performed using autogenous bone grafts harvesting the particulate bone from the iliac crest. All results have a high risk of confounding by indication. This means that the indication for treatment may be related to the risk of future health outcomes. The resulting imbalance in the underlying risk profile between treated and comparison groups can generate biased results.

Results

Early secondary bone grafting compared to late secondary bone grafting

There was no difference in eruption of the canine adjacent to the cleft measured 1 to 4 years after bonegrafting with iliac crest bone in the study of Nishihara et al (2014). Ony fill was studied by Rawashdeh (2007) in a mixed group of unilateral and bilateral clefts using the Kindelan grading scale. No statistics were performed to test for differences between groups. Descriptive results on rates per Kindelan grading were

overall comparable between both groups (example: Grade 1 after early secondary grafting was reported for 90% (unilateral) and 56.2% (bilateral) versus 80% (unilateral) and 57.1% (bilateral) after late secondary grafting). Freihofer (1993) measured success rate of the treatment defined as no oronasal communication and with at least 50 % of the bone graft height. They found that early secondary bone grafting gave significantly better results than late secondary bone grafting for both unilateral and bilateral clefts. Sindet-Pedersen (1985) evaluated the marginal bone-level for teeth adjacent to the cleft. They also concluded that early secondary bone grafting before eruption of the canine gave significantly better results.

Nishihara (2014) reported the number of patients that achieved an acceptable bony bridge was not significantly different between groups (p=0.16). Jia (2006) reported outcomes on interdental septal heights. Success was defined by the Bergland index Type I and II. Success was achieved significantly more frequently after early secondary bone grafting both for unilateral and bilateral clefts (p=0,049 and p=0,044). Failure of interdental septal heights, defined as Bergland index Type III and IV, was more prevalent after late secondary bone grafting but the differences were not significant.

Miller (2010) and Sindet-Pedersen (1985) reported results on fistulae, but the differences were not significant (Miller: Two out of 61 fistulae reported for early bone grafting and three out of 38 reported for in the late bone grafting group; Sindet-Pedersen: no fistulae for early secondary bone grafting before eruption of the canine and various [range 1-11] in other groups). Furthermore, Miller et al (2010) gave a detailed description of the observed complications besides fistulae, like pyogenic granuloma, residual alveolar defect without fistula; hip wound dehiscence; gingival hyperplasia, and fibroma. In addition, Jia (2006) reported one patient with chronic infection of the graft resulting in complete failure in the early bone graft group versus five in the late early bone grafting group. In the early bone graft group 9.8% participants had complications including fistulae compared to 13.2% in the late secondary bone graft group. Differences were not significant.

None of the studies reported the need for a second grave. Outcomes of interest that were not mentioned in the studies are: orthodontics related to bone graft, physiological shape of the alveolar process, and quality of life measures.

Secondary bone grafting compared to tertiary bone grafting

Trindade-Suedam (2012) reported on septal heights using the Bergland index. Two months after the intervention intermediate and palatal septal heights were significantly better in the secondary bone graft group. After six to twelve months the secondary bone grafting group reported significantly better outcomes for all measured septal heights (buccal, intermediate and palatal) than the group with tertiary bone grafting.

Freihoferet Al (1993) found that early secondary bone grafting gave significantly better results than tertiary bone grafting for both unilateral and bilateral clefts for closure of the oronasal communication and achieving at least 50 % of the bone graft height. Dempf (2002) provided descriptive results for bone height, which were slightly better for the secondary bone grafting group than after tertiary bone grafting. For example, 85% of the participants in the secondary group had a bone height score between 50 and 100% versus 68% in the tertiary group. On the other hand, infra-occlusion of the teeth adjacent to the bone gap was more frequently reported after secondary bone grafting (48%)vs. 30% in tertiary group). It is stated that a missing lateral incisor may lead to a vertical growth deficit. Loss of teeth adjacent to the cleft was reported for five patients

after tertiary bone grafting compared to none after secondary bone grafting. However, no statistical tests were performed for any of the outcomes. Dempf (2002) detected no functional relevant fistulae for both groups.

Grading the evidence
Grading the evidence started at the level of low evidence because all of the included studies had an observational design. Results were not upgraded for any outcome since no very large magnitude of effect was reported, none of the studies had properly controlled for confounding, and no dose-response effect was observed. Downgrading was, however, necessary as a result of sparse data and limitations of study designs (confounding by indication). The number of patients, and for some outcomes like complications the number of events, were very low. In addition, the study designs had major flaws like inclusion on follow up and drop-out rates above 35%.

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out on the following scientific question and associated PICO:

Is there a preference in terms of timing for bone grafting surgery in a patient with a CLA/P?
P: Patients with a (gnatho) CLA/P;
I: Early secondary closure of the cleft by bone grafting procedure (BIG);
C: Other times when BIG can be performed: 1. primary closure of the cleft during lip closure/gingivo periosteoplasty, 2. leave secondary closure and 3. tertiary closure;
O: Eruption (disorder) of the cuspidate on the CLA/P side (important), amount of bone remaining in the cleft (important), fistula formation, necessity for resurgery, physiological form of the alveolar process, pre/post-operative orthodontics: Expanding arch, growth, pain and quality of life.

Relevant outcome measurements
The working group considered the amount of bone remaining in the cleft, continuity of the alveolar process and absence of oro-nasal communication critical outcome measures for decision making; and eruption of the cuspidate and/or lateral incision on the CLA/P side and growth of the maxilla for decision making important outcome measures.
The working group did not define the aforementioned outcome measures a priori, but used the definitions used in the studies.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and March 12, 2014. This search aimed to identify systematic reviews, RCTs, ccts, and observational studies. Detailed search characteristics are shown in the appendix.

Studies that investigated patients with cleft lip, alveolus and palate were selected if they compared early secondary autogenous bone grafting to bone grafting performed at other developmental moments, like primary, late secondary, or tertiary. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: Eruption of the canine at the cleft side, bone height and amount of bone between

the nasal floor and the alveolar crest, fistulae, necessity for revisional grafting, orthodontics related to bone grafting, physiological shape of the alveolar process, periodontal condition of the teeth adjacent to the cleft, growth and quality of life measures. Studies that presented test results (p-value) without the size of the effect or association were excluded.

The initial search identified 445 references of which 15 were assessed full text.. Ten studies, all with a non-randomized observational study design, seemed to be relevant but two did not present data on the effect size or association for the outcomes of interest. Finally, eight studies were included. The evidence tables and risk of bias assessment are added as an appendix.

Reporting

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Technique of bone grafting procedure in patients with a CLA/P

Primary question

Is there a preference for a type of bone graft in the bone grafting procedure in a patient with uni- or bilateral cheilognatho (palato) CLA/P?

Recommendation

Reconstruct the alveolar CLA/P (bone grafting procedure) with pelvic cam bone or kinbot (possibly supplemented by a bone substitute).

Use pelvic cam bone for larger volumes required or choose to have kinbot supplemented with a bone substitute.

No recommendation on the choice of the bone substitute to be used can be made based on the literature.

The use of only a bone substitute for the reconstruction of an alveolar CLA/P, i.e. without an autologous bone graft, should only be investigated and is not yet generally used in practice.

Considerations

Filling the cleft with autologous bone is still the gold standard at the bone in gnatho procedure. Both iliac crest and kinbot are used for this purpose. Pelvic cam bone is a mesenchymal of origin and ossifies via a cartilage phase (enchondral). Kinbot is an ectomesenchymal of origin and survives without this cartilage phase. There is no evidence in the literature for the hypothesis used by some, that kinbot would therefore give better results. As pelvic cam bone and kinbot are both by far the most commonly used, other donor sites such as calvarium, tibia and rib have been excluded from this guideline.

Based on the literature consulted, it can be said that iliac crest and kinbot give similar results. The working group therefore concludes that both donor sites can be chosen. There is, however, a high degree of heterogeneity in the outcomes expressed, which makes a good comparison difficult. The important outcome measures, bone height and bone volume, are best measured using a (Cone beam) CT scan. This method has only recently been used and therefore has not been widely used. This measurement method was only used in 2 (Alonso, 2010; Canan, 2012) of the five studies. In the other three studies, this was measured using conventional X-rays which, however, only give a two-dimensional picture of the transplanted region.

In practice, the volume of the alveolar CLA/P tends to determine the choice of bone graft. In unilateral CLA/P, kinbot may be chosen, but in large volumes of the cleft such as in bilateral CLA/P, kinbot is not always sufficient (unless vomer bone is also used after osteotomy of the premaxilla).

Kinbot transplant only gives an intra-oral scar and does not have the co-morbidity sometimes associated with pelvic cam bone harvesting. Disadvantages of kinbot include possible damage to the permanent tooth elements in the lower front and neuropraxia of the mental nerve. In addition, the available amount, as already described, may be insufficient in large volumes of the cleft. This may be the case, in particular, when the procedure is performed early, when the permanent cuspidates in the lower jaw have not yet come through. This limits the bone volume to be harvested. Mixing this with a bone substitute can help. Pelvic cam bone as a donor site offers the advantage that there will always be sufficient volume. It can also be harvested simultaneously, depending on the setting, resulting in a reduction of OR time. No studies were found that could reliably assess the cost-effectiveness of pelvic cam bone versus kinbot, whether or not in combination with a bone substitute.

There is certainly room for the use of bone substitutes that aim to increase the volume of autologous bone graft used. In the contemporary literature, good successes are especially achieved with calcium phosphate matrices. The complete replacement of a bone graft by rhBMP2 for the filling of alveolar bone defect in gnathoCLA/P is not recommended for the time being due to the adverse side effects and the suboptimal dose-release curve (expert opinion N. G. Janssen based on Woo article, 2012 JOMS; “Adverse events reported after the use of recombinant human bone morphogenetic protein.”). Current research into other bone replacement materials, however, is hopeful for the future.

Substantiation Background

In patients with uni- or bilateral cheilognatho (palatoCLA/P), a bone graft is used for a cleft at a given time by means of the bone grafting procedure. This creates a bone bridge between both jaw segments, stabilizes them and thus supports the base of the ala nasi on the CLA/P side. In addition, any existing oronasal communication will be closed. Also, the cuspidate and/ or lateral incision on the CLA/P side is offered the possibility to erupt into the newly formed bone. The timing and technique of this procedure are important.

In the technique of bone grafting procedure, careful surgical tissue handling is important, as is the case for all surgical interventions in CLA/P. For example, it is essential that the mucoperiostal blades created are closed as watertight as possible. There is diversity in the choice of bone graft. In the Netherlands, pelvic cam bone (anterior iliac crest) or kinbot is often chosen as a donor bone. Sometimes this is mixed with a bone substitute. The purpose of this baseline question is to assess whether the use of a particular type of bone and/or bone substitute leads to better results and/or fewer complications in the bone grafting procedure.

Conclusions

Very low GRADE	We found very little proof that mandibular symphyseal bone grafting with a bone subsitute is more likely to result in a clinically relevant difference regarding bone volume filling percentage, maxillary height, and bone healing as compared to Iliac crest cancelling bone grafting. The overall outcome of iliac crest cancellous bone and mandibular symphysis bone to restore the alveolar cleft defects are comparable. *Enemark, 2001; Freihofer, 1993; Alonso, 2010; Canan, 2012; Thuaksuban, 2010*

Very low GRADE	We found very little proof that bone grafting with rhBMP2 on a resorbable collagen sponge is more likely to result in better dental eruption as compared to Iliac crest cancelling bone grafting. *Alonso, 2010, Canan, 2012*

Very low GRADE	We found very little proof that bone grafting with a bone substitute is more likely to result in better dental eruption as compared to Iliac crest cancellous bone grafting. *Alonso, 2010; Canan, 2012; Freihofer, 1993*

Very Low GRADE	We found very little proof that adding a bone substitute to an autogenous bone graft (mandibular symphysis) is more likely to give a better result in overall clinical outcome than using an autogenous bone graft alone. *Thuaksuban, 2010*

Summary of literature

Study characteristics

Two studies compared traditional iliac crest cancellous bone grafting to a resorbable collagen sponge impregnated with rhBMP-2 (Infuse Bone Graft kit (Medtronic, Memphis, Tenn.)) (Alonso, 2010; Canan, 2012). A study by Thuaksuban compared traditional iliac crest cancellous bone grafting to a composite of deproteinized bovine bone (DBB) and autogenous cancellous bone (Thuaksuban, 2010). Two studies compared traditional iliac crest cancellous bone grafting to mandibular bone grafting (Enemark, 2001; Freihofer, 1993).

Alonso (n=16; I:8 vs. C:8) as well as canan (n=12; I:6 vs. C:6) reported a follow-up of 12 months, Freihofer (n=296; I:123 vs. C:59) or at least 12 months, Thuaksuban (n=27; I:13 vs. C:14) or 24 months, and Enemark (n=57) or 4 years. In all studies the intervention group and the control group were comparable at baseline.

Results

Iliac crest cancellous bone grafting versus mandibular symphyseal bone grafting

Enemark (2001) reported no significant difference in terms of eruption disturbances between the mandibular

bone grafting group (31.8%) and the iliac crest bone grafting group (35.1%) (p> 0.05). Bone volume measured in Marginal Bone Level Scores, however, was significantly superior in the mandibular bone grafting group (1:13 vs. 1:33, p = 0,029). The number of complications was scarce, although both groups demonstrated some gingival retraction with a longer crown length at the cleft side central incisor.

Freihofer (1993) found significantly better success rates for mandibular symphyseal bone than for iliac crest bone grafting (92% vs. 46%, p < 0.05). Success was defined as obtaining no oronasal communication and with at least 50 % of the bone graft height.

Iliac crest cancellous bone grafting versus autogenous bone with a bone substitute or a solitary bone substitute without autogenous bone.
There was no difference in bone filling percentage after 12 months measured by Alonso (2010) and Canan (2012). Alonso reported a significant difference regarding maxillary height between the groups. The maxillary height in the bone-graft substitute group lagged behind compared to the group with iliac crest bone graft after 12 months (mean 10.2 mm vs. 13.9 mm, p = 0,001). By contrast, CANAN (2012) reported no difference on maxillary height. In both studies, there was no difference in bone healing (postoperative defect volume) between the groups after 12 months (Alonso and Canan et al). Alonso reported undisturbed dental eruption in both groups. No further details were described.

Thuaksuban found no statistically significant difference in average bone graft densities and heights between both groups at each time interval (Thuaksuban, 2010).

Grading the evidence
Grading the evidence regarding mandibular bone grafting started at the level of low evidence because all of the included studies had an observational design. Results were not upgraded for any outcome since no very large magnitude of effect was reported, none of the studies had properly controlled for confounding, and no dose-response effect was observed. Downgrading was, however, necessary as a result of sparse data and limitations of study designs (confounding by indication). The number of patients, and for some outcomes like complications, the number of events were very low.

Search and select

In order to answer the initial question, a systematic literature analysis was carried out with the following scientific question and associated PICO:

What are the advantages/disadvantages of the bone grafting procedure with pelvic cam bone compared to this procedure with kinbot (whether or not in combination with a bone substitute) in a patient with a gnathoCLA/P?
P: Patients with a (gnatho) CLA/P;
I: bone grafting procedure with pelvic cam bone;
C: Bone grafting procedure with kinbot in combination with or without a bone substitute. Or the bone grafting procedure with a bone substitute only;
O: Bone volume (bone filling percentage), jaw height (maxillary height), eruption (disorder) of the cuspidate or lateral incision, postoperative complications such as fistula formation, need for re-operation,

process form, pre /post-operative orthodontics: expanding dental arch, donor site morbidity, recovery of the apertura piriformis, pain, quality of life.

Relevant outcome measurements
The working group considers eruption (disorder) of the cuspidate and/or lateral incision to be a critical outcome measure for decision-making; also bone volume (bone filling percentage), jaw height (maxillary height) and postoperative complications are important outcome measures for decision-making.
The working group did not define the aforementioned outcome measures a priori, but used the definitions used in the studies.

Search and study selection (methods)
A systematic search was performed using the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and March 12, 2014. This search aimed to identify systematic reviews, RCTs, ccts and observational studies. Detailed search characteristics are summarized in the appendix.

Studies that investigated patients with cleft lip and palate were selected if they compared traditional iliac crest cancellous bone grafting to mandibular bone grafting or autogenous bone with a bone substitute. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: bone filling percentage, maxillary height, dental eruption, or postoperative complications.

The initial search identified 240 references of which 8 were assessed full text.. Five studies, all with a non-randomized observational study design, seemed to be relevant but did not present data on the effect size or association for the outcomes of interest. Finally, five studies were included. The evidence tables and risk of bias assessment are added as the appendix.

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Orthodontics in patients with a CLA/P

This module is divided into the following sub-modules:

- Nasoalveolar molding in CLA/P
- Ventral traction in CLA/P
- Retention in CLA/P
- Le Fort I vs distraction at CLA/P

Reporting

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Orthodontics: Nasoalveolar molding (NAM) in CLA/P

Primary question

Is there an indication for nasoalveolar molding in patients with complete unilateral or bilateral cheilognathopalatoCLA/P?

Recommendation

Be cautious about the use of NAM in infants with a complete unilateral or bilateral cheilognathopalatoCLA/P and PAS WAS in principle only increased in preparation for or in a clinical trial.

Considerations

Although NAM has now been part of the multidisciplinary treatment of babies with CLA/P in CentrEs worldwide for over 20 years, very little research of good quality can be found on this therapy. The working group identified two recent studies (Liang, 2016; Shetty, 2017) in which the shape of the nose (Liang, 2016) and the shape of the upper arch are examined after NAM (Shetty, 2017). Both studies are methodologically of very poor quality. Other potentially beneficial or adverse effects of NAM have not been (yet) reported in the literature in high-quality studies. Thus, evidence-based recommendations for the use of NAM do not appear to be possible on the basis of THE current literature.

The working group therefore consulted the Special Interest Group Orthodontie (SIG Orthodontie) of the Dutch Association for CLA/P and Craniofacial Discrepancies (February 2018). This brings together all orthodontists in the Netherlands who treat children with CLA/P on a regular basis.

The respondents have all TAKEN note of NAM, but realize that there is no evidence for this therapy to date. NAM is not used by any of the respondents. The ski orthodontists are very reluctant because of the lack of scientific evidence and because of the cost of treatment and even more because of the increase in 'burden of care' for the parents when there is no proven effectiveness. It is stressed that good clinical research is urgently needed.

The question that was central to this section of the directive ''Is there any indication for this in patients with a complete unilateral or bilateral cheilognathopalatoCLA/P?'' as things stand at the moment, neither denial nor affirmative can be answered. In addition, the considerations should be taken into account that NAM is LaBour-intensive for parents and orthodontist given the frequent treatment sessions that this treatment requires and increases the cost of the total treatment, while the effectiveness has not been proven. On the other hand, at least no negative effects on the development of the jaw arc, the shape of the nose and the aesthetic results have been reported in the literature so far.

A search in some international clinical trial registers (see below) shows that there are currently no trials in progress from which an answer can be expected. A randomized controlled study comparing NAM with another intervention or non-intervention requires equivalent experience in both interventions. The recently published results of the Scandcleft trial have that added

Underlined: difference in surgeon experience for the interventions in the arms of the trial affected the results in this trial (Rautio, 2017; Shaw, 2017). Therefore, the working group recommends that NAM may be used in preparation for a trial.

In view of the multitude of parameters, which need a response, the working group suggests being reluctant to TAKE into babies with unilateral or bilateral cheilognathopalatoCLA/P and to carry out further randomized clinical studies before more robust recommendations can be made on the indication for NAM.

Substantiation Background

Neonatal Infant Orthopedics (IO) aims to better position the upper jaw segments with a palate plate relative to each other in patients with complete unilateral or bilateral cheilognathopalatoCLA/P (UCLP/BCLP). In addition, many other purposes of this therapy have been mentioned in the literature (Hosseini, 2017). In the Netherlands, a 'landmark' randomized controlled trial (RCT) was done (DUTCHCLEFT (2001)) for effects of IO versus no IO with a passive palate in children with a UCLP up to 12 years of age. The study showed that IO has no long-term added value (Kuijpers-Jagtman, 2013). After that, all CentrEs in the Netherlands have almost abandoned this therapy in children with a UCLP, while it is still used in patients with a BCLP. At the same time nasoalveolar molding (NAM) - also written as molding - occurred, with nasal stents added to the palate to achieve a better shape of the nose after which a surgical lip closure is performed with or without periosteoplasty of the jaw crevice (Maull, 1999). In the Netherlands this therapy is almost not applied but worldwide there is a heated debate about the usefulness of NAM.

Conclusions

Very low GRADE	We found very low quality evidence that NAM, compared to no NAM, is associated with no differences in nasal shape and symmetry of patients with a complete unilateral cleft lip and palate. *Sources (Liang, 2016)*

- GRADE	We found inssuficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on psychosocial wellbeing of parents of patients with a complete unilateral or bilateral cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on esthetic outcome of patients with a complete unilateral or bilateral cleft lip and palate.

- **GRADE**	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on cost effectiveness of patients with a complete unilateral or bilateral cleft lip and palate.

- **GRADE**	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on facilitation of surgery of patients with a complete unilateral or bilateral cleft lip and palate.

Very low GRADE	We found very low quality evidence that NAM, compared to no NAM, is associated with no difference in maxillary arch dimensions of patients with a complete unilateral cleft lip and palate. *Sources (Shetty, 2017)*

- **GRADE**	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on cross bite of patients with a complete unilateral or bilateral cleft lip and palate.

- **GRADE**	We found insufficient evidence to formulate a conclusion on the effect of NAM, compared to no NAM, on maxillofacial growth of patients with a complete unilateral or bilateral cleft lip and palate.

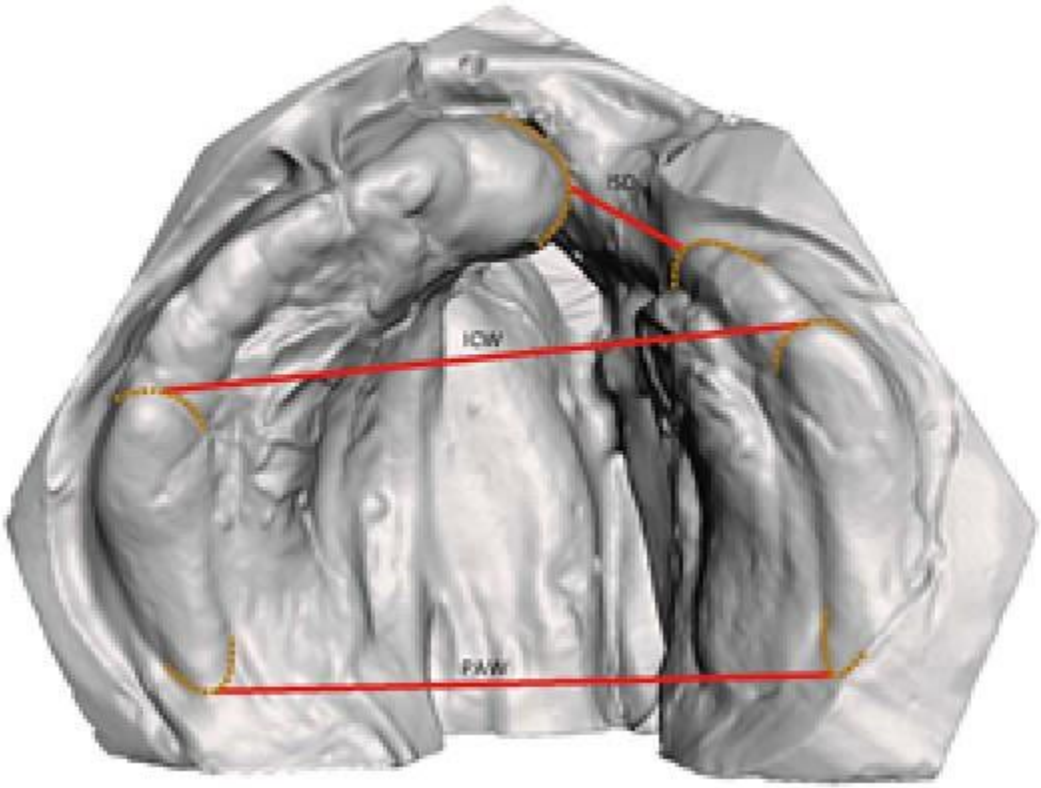
Summary of literature

Study description
A total of 2 studies are included in this literature summary (Liang, 2016; Shetty, 2017).

Liang (2016) is a study that compares the effect of NAM (n=42) versus no NAM (n=42) on long-term nasal shape and symmetry in patients with complete non-syndromic UCLP. The allocation of treatment was based on time period of investigation. All patients that entered the hospital in 2001 had no NAM. All patients that entered the hospital between 2008 and 2010 received NAM. The treatment started between 24 to 61 days (mean age 33 days). The duration of the NAM ranged from 36 to 104 days (mean 72 days). After that, primary cheiloplasty was performed without nasal cartilage dissection at a mean age of 113 days in the NAM group. In the no-NAM group the same surgical procedure was followed by the same surgeon at a mean age of 109 days. A score for nasal shape and symmetry was based on full-face and submental photographs tasks 4 to 5 years postoperatively. A panel of 10 professionals from different medical disciplines rated full face frontal pictures for the position of the alar base, and symmetry of the nasal dome and nasolabial fold. On submental oblique facial photographs, the panel rated symmetry of the nasal dome and nostrils, length of the columella, and shape of the nostril sill and tip of the nose. A score ranging from 1-5 per picture was calculated (1= poor; 2= fair; 3= average; 4= good; and 5= excellent). The score of the two pictures was combined into a total score (2 to 10) per patient. The professionals were blinded for the type of treatment. The procedure resulted in a total score between 20 to 100 points per patient.

Shetty (2017) is a study investigating the long-term effect of NAM (n=60) versus no NAM (n=60) on the growth of the maxillary arch in patients with UCLP at different ages. The randomization of participants to the study versus control group was not described in the article. The intervention group was divided into three subgroups (I: NAM initiated within 1 month, II: Between 1 and 6 months, III: Between 6 and 12 months). NAM was started at 11 days (range 1 to 28) in subgroup I, 94 days (range 33 to 180) in subgroup II and 235 days (range 180 to 365) in subgroup III. Patients with UCLP in subgroup I were treated with NAM until 6 months of age and in subgroup II and III for a minimum of 3 months. The control group was also divided into three groups (I: Underwent operation at 6 months of age, II: Between 6 and 9 months of age, III: Between 9 and 15 months of age). Cheiloplasty was performed at the same time in the case and control group. Palatoplasty was performed in both groups at 18 months.

Figure 1



Modified from Shetty (2017) (courtesy Robin Bruggink, Radboudumc). To quantify maxillary arch dimensions 3 distances were measured: Intersegment distance (ISD, compares to alveolar cleft width), intercanine width (ICW) and posterior arch width (PAW) at first visit (T1), before cheiloplasty (T2) and at 6 years (T3)

Results

Nasal shape and symmetry

The reliability coefficient was α= 0,925, indicating measurement consistency among the medical professionals. The mean score ± SD was 66.62 ± 14.25 and 66.31 ± 15.08 in the NAM and no NAM group respectively. The difference between the groups was not statistically different (F= 0,009, P= 0,923) (Liang, 2016).

Evidentiary value of literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with three levels was, however, necessary as there were limitations in study design (no adequate randomization, no allocation concealment, no blinding of care providers and patients), there was indirect evidence (participants with a specific ethnicity) and imprecision (small sample size).

Psychosocial well-being of the parents

Differences in psychosocial well-being between parents of both groups were not assessed in the included study.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found investigating differences in psychosocial wellbeing between parents of both groups.

Esthetic outcome

Differences in esthetic outcomes between both groups were not assessed in the included studies.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found investigating differences in esthetic outcome between both groups.

Cost effectiveness

Differences in cost effectiveness between both groups were not assessed in the included studies.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found investigating differences in cost effectiveness between parents of both groups.

Facilitation of surgery

Differences in facilitation of surgery between both groups were not assessed in the included studies.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found investigating differences in facilitation of surgery between both groups.

Shape of upper arch

The distance ISD was not significantly different between the NAM and the control groups at T1 and T3, but was significantly narrower in the NAM-groups at T2 (Mean difference (95% CI) I: -11.45 (-12.54, -10.37); II: -8.00 (-9.26, -6.74); III: -6.80 (-8.10, -5.51). The ICW was not significantly different between the NAM and control groups at T1 and T2, but was significantly different at T3 (Mean difference (95% CI) I: 3.30 (2.56, 4.04); II: 2.15 (1.31, 2.99); III: 1.15 (0.18, 2.12)). The PAW was not significantly different between the study and control group at T1, T2 and T3 (Shetty, 2017).

The change in mean ISD between T1 and T2 and T2 and T3 was significantly different in the study group

versus the control group in all subgroups. The change in mean ICW between T1 and T2, T2 and T3, and T1 and T3 was also significantly different in the study group versus the control group in all subgroups (except between T1 and T2 in subgroup I). No statistical differences were found in mean PAW between T1 and T2, T2 and T3, and T1 and T3 in the study versus control group in all subgroups (except between T2 and T3 in subgroup III) (Shetty, 2017).

Evidentiary value of literature
Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with three levels was, however, necessary as there were limitations in study design (no adequate randomization and no allocation concealment), there was indirect evidence (participants with a specific ethnicity) and imprecision (small sample size).

Cross bite
Differences in cross bite between both groups were not assessed in the included study.

Evidentiary value of literature
Grading the evidence was not possible, because no articles were found investigating differences in cross bite between both groups.

Maxillofacial growth
Differences in maxillofacial growth between both groups were not assessed in the included study.

Evidentiary value of literature
Grading the evidence was not possible, because no articles were found investigating differences in cross bite between both groups.

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out on the following question:
What are the effects of NAM compared to NAM or NAM compared to neonatal infant orthopedics without nasal stents, in patients with complete unilateral or bilateral CLA/P?

P: Patients with complete unilateral or bilateral cheilognathopalatoCLA/P; I: Nasoalveolar mo(u)lding;
C: No nasoalveolar mo(u)lding or infant orthopedics without nasal stents;
O: Shape and symmetry of the nose; psychosocial well-being of the parents; aesthetic outcome; cost-effectiveness; facilitation of surgery; shape of the arch; frequency of cross bite, maxillofacial growth.

Relevant outcome measurements
The working group considered shape and function of the nose and aesthetic outcome for decision-making critical outcome measures; facilitation of lip surgery, psychosocial well-being of parents and cost-effectiveness for decision-making important outcome measures. The working group did not define a priori

the aforementioned outcome measures, but used the definitions used in the studies. The workgroup did not define any clinically (patient) relevant differences.

Search and Select (Method)

A systematic search was performed in the databases of Medline (through OVID) and Embase (though Embase.com) between 1993 and August 11th, 2017. This search aimed to identify published systematic reviews, RCTs and controlled clinical trials (CCT). The search strategy is described under the tab “Accountability”.

Studies that investigated the effectiveness of NAM compared to no NAM and no IO in patients with a complete unilateral or bilateral cleft were selected. The initial search identified 479 references of which 134 were assessed full text.. After assessment of full text 132 studies were excluded and 2 studies included.
Reasons for exclusion are described in the exclusion table.

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Orthodontic treatment in patients with CLA/P - ventral traction

Primary question

When should ventral traction of the upper jaw be applied in children with a (cheilognatho) palatoCLA/P?

Sub-questions:
What considerations play a role in the choice of ventral traction on the upper jaw in children with cheilognatho, cheilognathopalato or palatoCLA/P and what is the best time to do this?

Is there a preference for a particular technique of ventral traction on the upper jaw?

Recommendation

In principle, do not apply ventral traction to the upper jaw with a facemask on a dental anchored orthodontic device in children with CLA/P in whom the forward growth of the upper jaw is deficient.

Consider ventral traction with a facemask on a dental anchored orthodontic device at:

1. slight underdevelopment of the upper jaw or;
2. if the patient and/or parents do not require surgical treatment, or
3. if the patient has a number of favorable characteristics. Guidance may include:

    - patient between five and nine years of age;
    - Mild skeletal abnormality ANB < -10 at pre-age normal SNB angle; facial aesthetics minimal
    - abnormalities;
    - convergent growth pattern with low lower face half;
    - AP displacement of the lower jaw in habitual occlusion (protral forced bite); symmetrical condylar
    - growth;
    - no hyperplasia of the mandible in the family;
    - good co-operation with the orthodontic treatment is expected.

If ventral traction is applied with a facemask to a dental anchored device:

Inform the patient and parents that the effect may be limited and that it will not be clear at the end of the growth period whether osteotomy of the upper jaw will still be necessary.

Considerations

Various methods of ventral traction on the upper jaw in patients with CLA/P are described in the literature. However, very limited literature with a very low level of evidence is available describing long-term results of ventral traction, with patients being continued until the

facial growth was complete. The opinion in this guideline is therefore based mainly on expert opinion and partly on side effects on the lower jaw in children without CLA/P described in the literature.

In the treatment of underdevelopment of the upper jaw, the patient wears elastic bands from an extra-orally worn facemask to an intra-oral orthodontic device anchored to the dentition. In this form of ventral traction, the forces are actually transmitted via the periodontal ligament of the dental elements to the maxillary bone and the sutures around the upper jaw. As a result, part of the jaw relationship correction is of dentoalveolar and not of skeletal origin. A meta-analysis in children with an underdevelopment of the upper jaw without a CLA/P in which three randomized controlled trials could be included showed that in addition to a forward effect on the upper jaw, reverse displacement of the lower jaw with a 'clockwise' rotation of the mandibular plane and a 'counterclockwise' rotation of the palatinal plane (Cordasco, 2014). These effects lead to an extension of the lower face half. It also describes the mesial movement of the first molars in the upper jaw, protrusion of the upper incisions and retrusion of the lower incisions (Kim, 1999; MacDonald, 1999; Jäger, 2001). There is no reason to believe that the effects on the lower jaw and the lower face half in children with a CLA/P would be different. Both the above mentioned systematic review of Cordasco, 2014 and also in the Cochrane Review of Watkinson, 2013 concerning children without CLA/P, also concluded that no statement can be made about the long-term efficacy of the facial orthopedic treatment of underdevelopment of the upper jaw. The same is apparent from the literature review carried out for this Directive on children with CLA/P.

After the literature review for this guideline was completed, a systematic review of Foersch (2015) was published that deals with maxillary protraction in Class III patients without CLA/P in combination with expansion or expansion/compression of the upper jaw according to an Alt-RAMEC protocol as proposed by Liou and Tsai (2005). The purpose of the expansion prior to the maxillary protraction is to open the sutures around the maxilla. The results show that maxillary protraction in combination with expansion does not have a significantly greater effect on the ventricular growth of the upper jaw than protraction alone. However, alternating expansion and compression (Alt-RAMEC) results in a greater ventral movement of the maxilla. For the time being, it is unknown to what extent this also applies to patients with CLA/P.

With ventral traction on the upper jaw, an attempt is made at the skeletal level to influence the growth of the upper jaw with as little dental side effects as possible. A new possibility is the use of skeletal anchorage in the upper jaw in the form of bone anchors or bone screws. With the introduction of skeletal anchorage by means of bone anchors it became possible to apply the forward traction forces of the facemask directly to the bone of the upper jaw. De Clerck (2009) introduced a method in which it is no longer necessary to carry an external facemask. In this treatment method, the forces are applied completely intra-orally via elastic bands that are worn 24 hours a day between bone anchors in the lower and upper jaws. The technique is called bone anchored maxillary protraction (BAMP). Bone anchors are placed bilaterally on the zygomaticoalveolar crista in the upper jaw and buccally on the alveolar process in the lower jaw between the lateral incisor and cuspid. Case series studies with BAMP in children without a CLA/P show a beneficial but very variable effect on the upper jaw of an average of 3.7 mm forward displacement with minimal dental effects (Baccetti,

2004; Nguyen, 2011). Also, conversion of the glenoidalis fossa was observed leading to a more backward position of the lower jaw (the Clerck, 2012). However, long-term results of BAMP are not yet available. In a recent overview of the results of BAMP (2015), De Clerck states that a positive effect can be expected (for which he does not provide any evidence) with regard to the application of BAMP. However, it is not yet clear to what extent BAMP is able to avoid the effect of scar tissue on growth.

Studies in children with CLA/P are currently ongoing in various centers around the world, but there is no way to judge the effect of BAMP in this group.

The working group considers that, in the current state of science, ventral traction on the upper jaw using a facemask on dental anchored equipment should in principle not be applied to patients with CLA/P. In the long term, ventral traction on the upper jaw on dental anchored equipment is unlikely to achieve the intended result and the result of surgery of the upper jaw is likely to be better.

Exceptions to the general advice not to apply ventral traction with a facemask to dental anchored equipment are those cases where the patient and/or parents do not wish to have jaw surgery. It may also be considered to apply active ventral traction to the upper jaw on tooth anchored equipment for a period of up to 12 to 18 months in the event of minor underdevelopment of the upper jaw at an early age. The table below presents a number of positive and negative factors based on expert opinion, which can be used as a guide.

Favorable factors	**Unfavorable factors**
Patient between 5 and 9 years old	Patient > 12 years
Mild skeletal abnormality ANB < -1^0 at a normal SNB angle for that age	Severe skeletal abnormality ANB > -1^0 and a larger SNB angle for that age
Aesthetics of the face are minimally abnormal	Aesthetics of the face disturbed
Convergent growth pattern with low bottom face half	Divergent growth pattern with normal/high lower face half
AP movement of the lower jaw in habitual occlusion (protral forced bite)	No AP shift of the lower jaw
Symmetrical condylar growth	Asymmetrical condylar growth
No hyperplasia of the mandibula in the family	Mandibular hyperplasia in the family
Good cooperation with orthodontic treatment expected	Good cooperation unlikely

In such borderline cases, ventral traction on dental anchored equipment may be considered as this treatment may potentially prevent surgical treatment. In this case, the patient and parents should be well informed about the treatment and the uncertainty about

long-term results. **Substantiation**

Background

In patients with cheilognathopalatoCLA/P, growth of the upper jaw may be disturbed in three dimensions. A disturbed ventral (forward) growth leads to an underdevelopment of the upper jaw in the sagittal sense which is often clearly visible in the face and gives the patient a characteristic 'CLA/P' face. This often manifests at a young age. Such underdevelopment of the upper jaw may be corrected by an upper maxillary osteotomy or surgical distraction at the end of the growth period.

Another possibility is to adjust the upper jaw growth early in life and if possible, avoid osteotomy later in life or reduce the osteotomy-bridged sagittal discrepancy. In the 1980s and 1990s, a technique was introduced that exerts extra-oral traction on the upper jaw to stimulate the growth of the sutures around the maxilla. An essential part of this treatment strategy is that it is already being used in the milk teeth. Later therapies were developed, which in combination with maxillary expansion and/or skeletal anchorage can also be applied in the mixture of baby and permanent teeth. It is important to know at what age ventral traction is most effective in terms of a stable result at the end of the growth phase of the face and which technique is preferred.

Conclusions

Very low GRADE	There is a very low level of evidence that loosening of the circummaxillary sutures (Alt- RAMEC approach) followed by maxillary protraction as a late treatment (at the age of 13-14 years) for unilateral cleft lip and palate patients produces a combination of skeletal changes (protraction of the maxilla, improvement of the jaw relationship) and dental compensations (counterclockwise rotation of the occlusal plane, retroclination of mandibular incisors) and is also associated with some unwanted tooth movements (open bite tendency, mandibular incisors retroclination). *Borzabadi-Farahani, 2014*

Very low GRADE	It is unclear what the effects are of maxillary protraction as an early treatment (on average 8 years old) for unilateral cleft lip and palate patients on maxillary growth. *Susami, 2014*

Summary of literature

Study characteristics
Two retrospective observational studies were included. Borzabadi-Farahani (2014) assessed the dentoskeletal effect of late maxillary protraction (MP) in patients with unilateral cleft lip and palate versus a control group of

untreated unilateral cleft lip and palate patients. The study group was comprised of 18 patients (Asian, Hispanic, Caucasian, and African-American background), and the control group of 17 patients. Lip repair was performed at 3 months of age using the Millard technique and the palate was closed with greater palatine flaps at 10-12 months. The Alt-RAMEC approach (Liou and Tsai, 2005) was used to loosen the circummaxillary sutures prior to application of maxillary protraction. The maxillary expansion and compression rate were set at 1 mm per day. This protocol was followed by full-time wear of Class III elastics and nighttime wear of a reverse pull headgear. Lateral cephalograms were tasks at the age of 13 to 14 years (T1) and also at 17-18 years (T2).

The study reports a statistically significant change across time between the MP-group and the control group for 10 cephalometric variables (values mean diff in MP group between T2-T1):
SNA (°): 1.95 (95% CI: 0.75 – 3.15); A ⊥ Na Perp (mm): 1.82 (95% CI: 0.86 – 2.77); CoA (mm): 2.92 (95% CI: 1.53 – 4.31); ANB(°): 3.13 (95% CI: 2.02 – 4.24); Wits (mm): 7.82 (5.01 – 10.54); MX-MD Diff (mm): 0.62 (95% CI: -1.58 – 2.83); Occl Plane-SN(°): -3.98 (95% CI: -5.99 - -1.98); Overjet (mm) 8.82 (95% CI: 5.90 – 11.74); FMIA (°): 4.05 (95% CI: -0.05 – 8.15); and IMPA (°): -5.77 (95% CI: -9.74 - -1.80). Late maxillary protraction created a slight open bite (0.66mm). Trends for overeruption of mandibular incisors and an increased lower face height (p=0.07 for both) were noted in the study group. Figure 1 and 2 copied from the study demonstrate the cephalometric landmarks and main cephalometric planes and measurements used in this study and elucidate the abbreviations used in the text above.

The results showed that Alt-RAMEC followed by late maxillary protraction in unilateral cleft lip and palate had a combined skeletal and dental effect (protraction of maxilla, improvement of the skeletal jaw relationship and dental compensations like counterclockwise rotation of the occlusal plane, retroclination of mandibular incisors, open bite tendency) in patients with UCLP.

Susami (2014) described the short- and long- term effects of maxillary protraction (MP) in mixed dentition patients with unilateral cleft lip and palate. In this study 11 Japanese patients were treated with maxillary protraction and followed until the completion of growth. The lip had been repaired at 3 to 6 months of age using the modified Millard technique and the palate was closed at 12 to 24 months using a pushback method in all cases. Mean age at the start of treatment was 8y10m, the mean duration of maxillary protraction was 3y7m. The mean age at the end of the observation period was 18y0m (mean length of follow-up 9y2m). The intra-oral appliance was a lingual arch with buccal extension arms and a facial mask was applied during nighttime (force 150-200 GF per side during 8-10 hrs). Full fixed appliance treatment was performed after MP in all patients. Lateral cephalograms were tasks before and after MP and after completion of growth.

The authors report a large variation in the effects of MP. Eventually, 5 out of 11 patients treated with MP required orthognathic surgery. The overjet improved to within normal limits in the six cases that did not require orthognathic surgery, but a large negative overjet was found in the remaining 5 cases immediately before orthognathic surgery. On average, the overbite had decreased after MP treatment, although the decrease was not significant.

To illustrate cephalometric changes several figures and tables are copied from the paper, see below. Figure 3 illustrates the angular and linear measurements, Wits appraisal and incisal relationship. Figure 4 shows reference lines and measurements of the antero-posterior positions of point A (A), pogonion (Pog) and

Maxillary first molar (U6). Table 2 shows the average changes in cephalometric measurements.

Figure 1. Cephalometric landmarks used in the study.

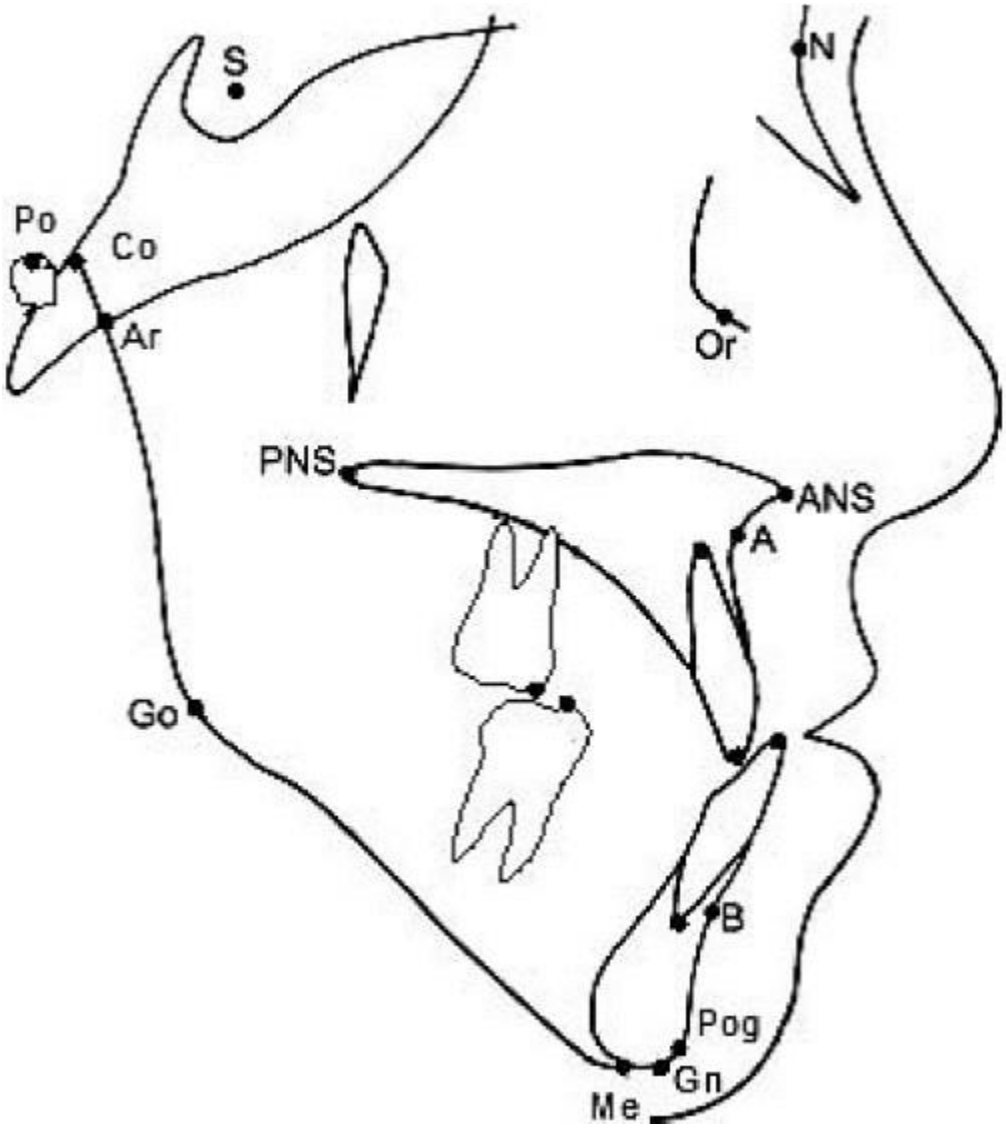
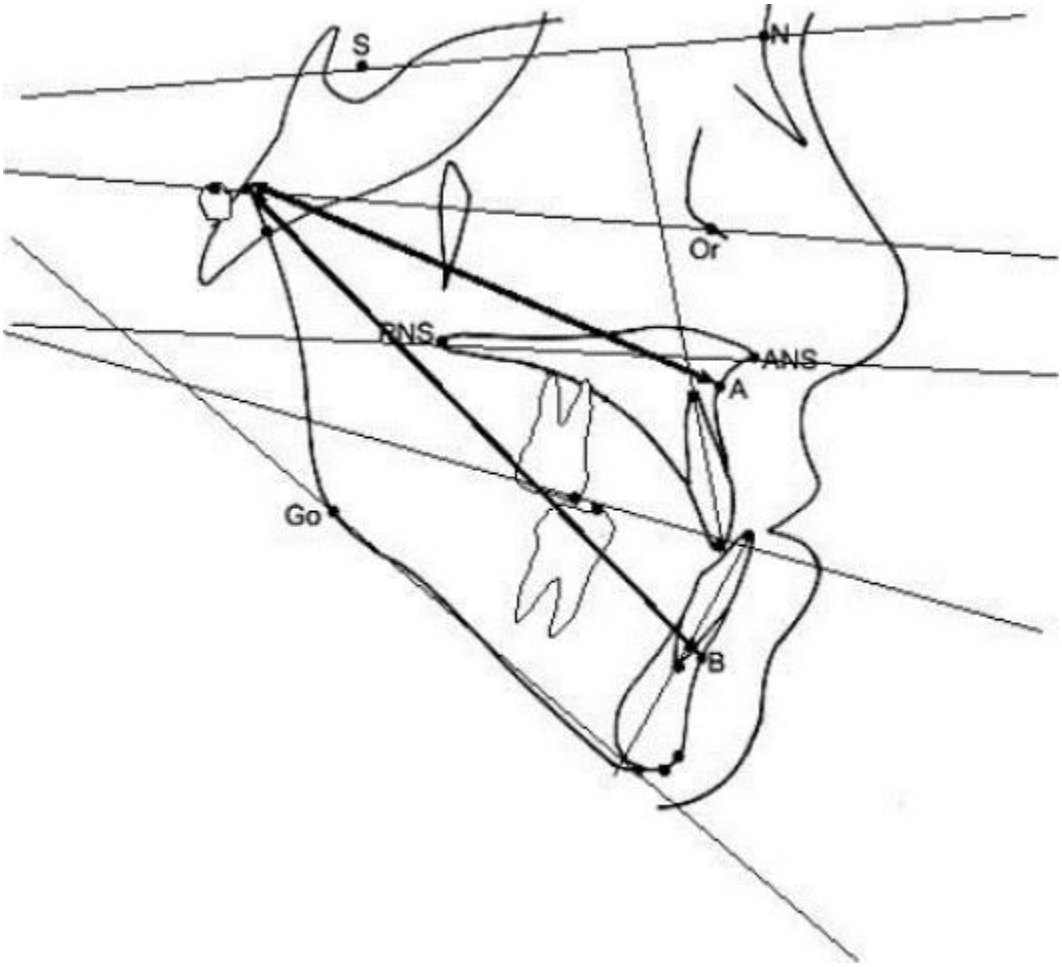
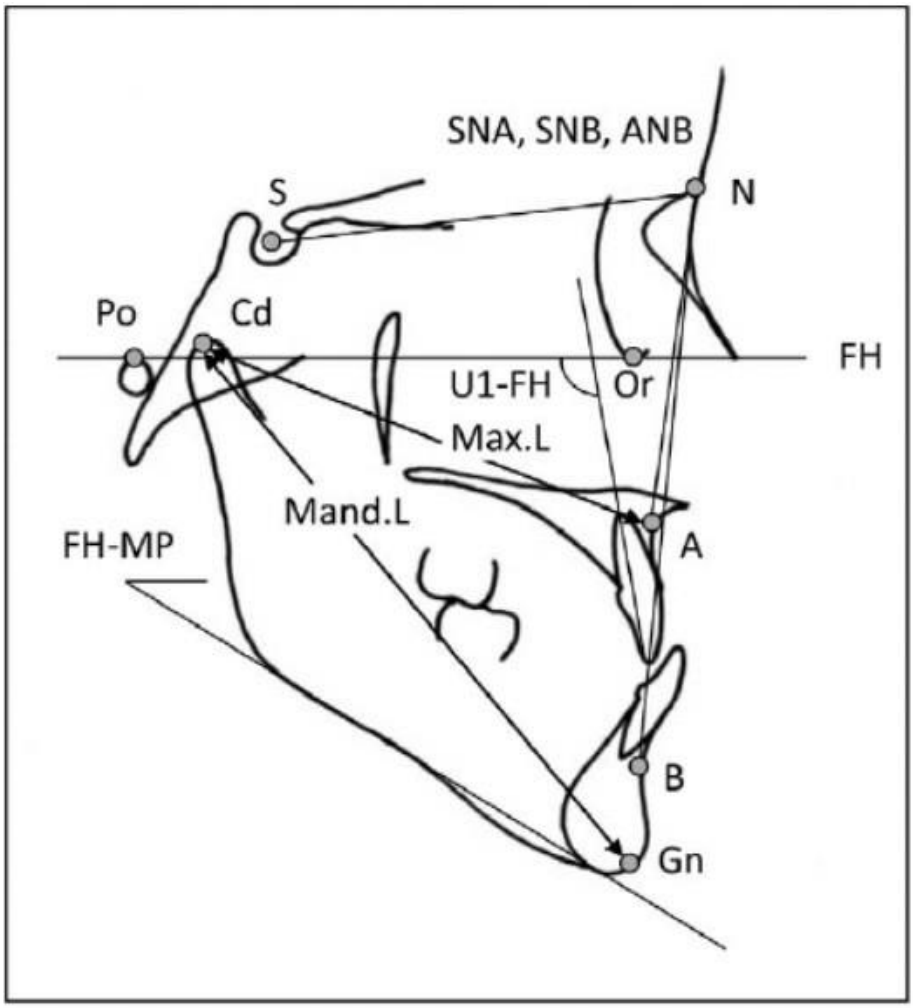


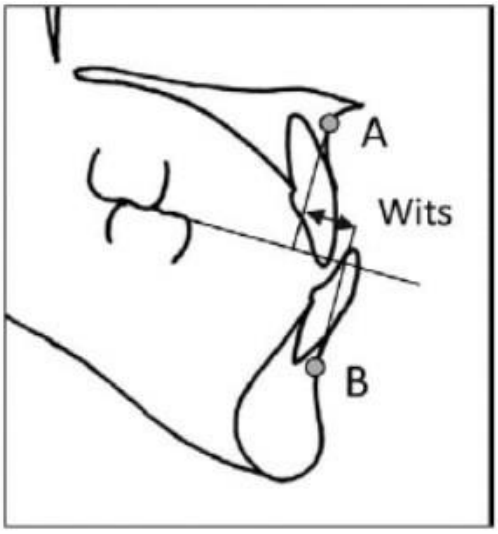
Figure 2. Main cephalometric planes and measurements of interest used in the study.

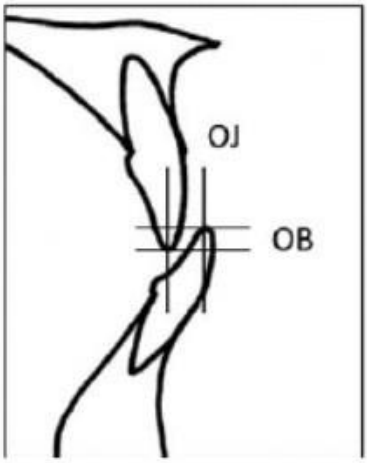


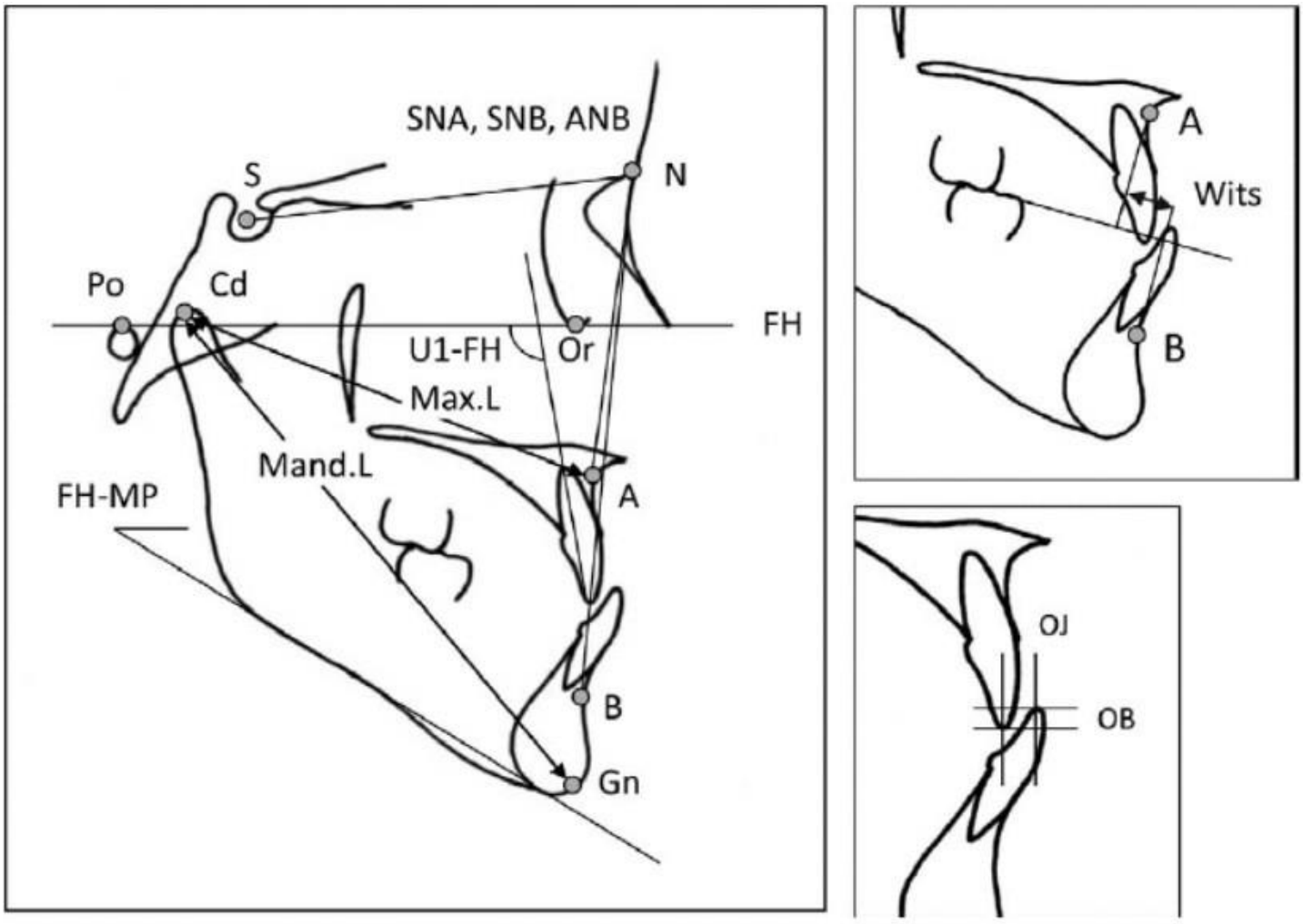
COA, midface length; Cogn, mandibular lengths; MX-MD Diff, Cogn-CoA; SN, anterior cranial base; PP, palatal plane; OCCL P, occlusal plane; MP, mandibular plane; FHP, Frankfort Horizontal Plane; A -Na Perp, length describing the sagitttal position of the maxilla; POG -Na Perp, length describing the sagittal position of the mandible; Y axis, the angle between SGN and SN; UFH, upper face height (N-ANS); LFH, lower height (ANS-Me); TFH, total face height (N-Me); Max Incisors-SN (°), the angle between the maxillary incisors and the anterior cranial base; FMIA, the angle between the mandibular incisors and the FHP; IMPA, the angle between the mandibular incisors and the mandibular plane.

Figure 3. Angular and linear measurements, Wits appraisal and incisal relationship.


SNA, SNB, ANB
S
N
Po
Cd
FH
U1-FH
Or
Max.L
Mand.L
FH-MP
A
B
Gn

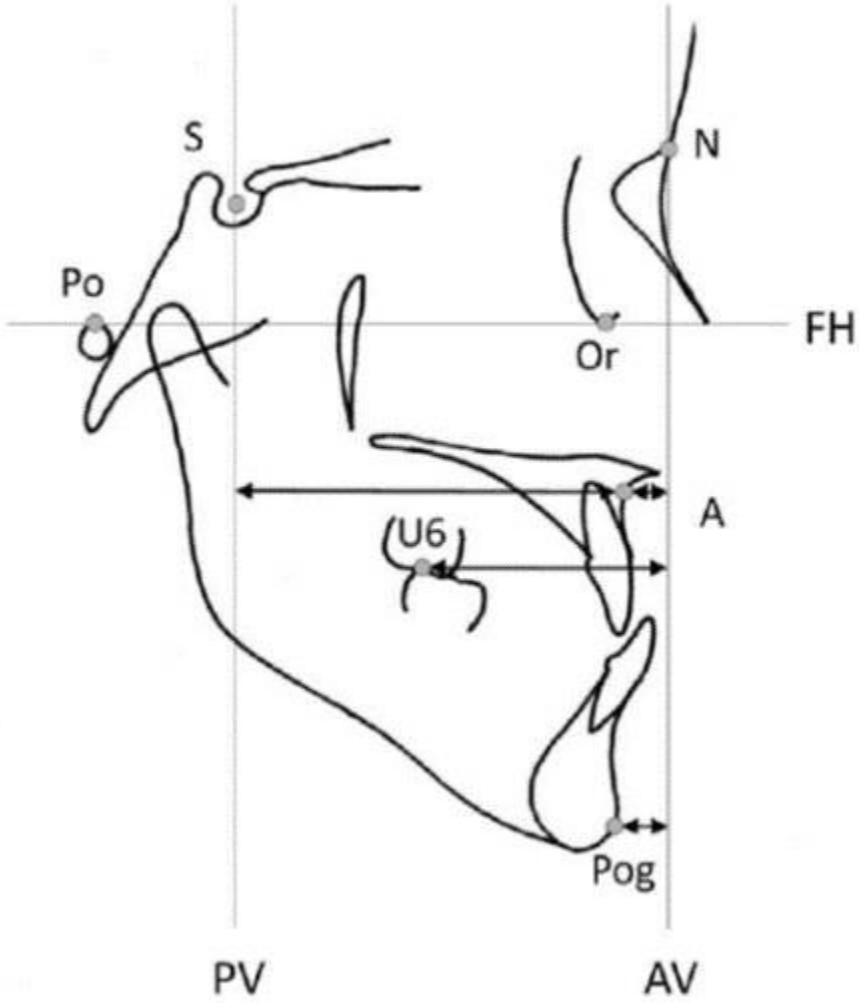

A
Wits
B

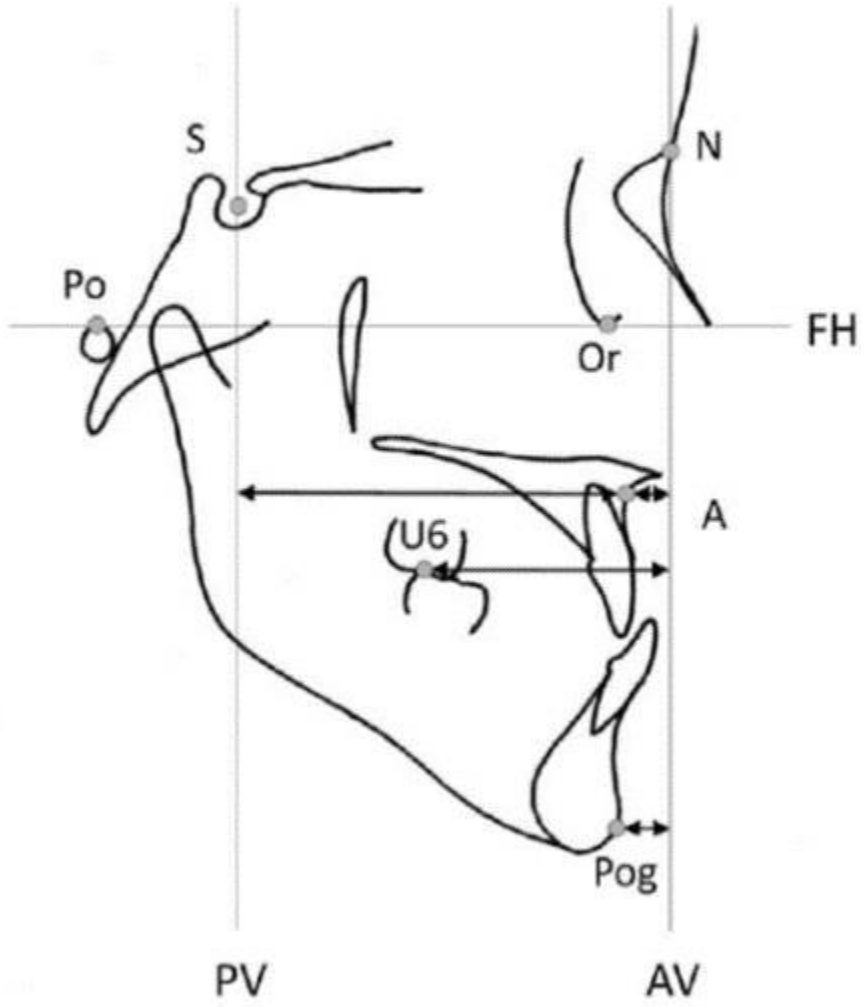

OJ
OB



N = nasion; S = Sella; Or = orbital; Po = porion; A = point A; B = point B; Cd = condylion; GN = gnathion; FH = frankfurt plane. SNA, SNB, ANB, Frankfurt mandibular plane angle (FH0MP), maxillary length (CD-A), mandibular length (CD-GN), Wits value (WITS), upper incisor inclination (U1-FH), overjet (OJ), and overbite (OB) were measured.

Figure 4. Reference lines and measurements of the antero-posterior positions of point A (A), pogonion (Pog) and maxillary first molar (U6).


S
N
Po
FH
Or
A
U6
Pog
PV
AV



N = nasion; S = sella; Or = orbitae; Po = porion; A = point A; Pog = pogonion; U6 = maxillary first molar. The Frankfurt plane (FH) served as the horizontal reference line, and two lines perpendicular to FH were used as the vertical reference lines. PV = posterior vertical reference line through sella; AV =
anterior vertical reference line through nasion;
Horizontal distances between point A and PV (A-PV), point A and AV (A-AV), U6 and AV (U6 – AV) and Pog and AV (Pog-AV) were measured.

Table 2. Average changes in cephalometric measurements

-	*Start or MP*	*End or MP*	*After Growth*
Parameter	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
A-PV (mm)	60.2 (3.1)	62.2 (3.6)	62.1 (4.4)
A-AV (mm)	-5.6 (2.2)	-5.6 (1.7)	-7.9 (2.0)
SNA (°)	76.6 (2.6)	76.5 (2.6)	73.9 (2.5)
Max. L (mm)	79.1 (3.5)	83.2 (4.0)	84.1 (4.8)
POG-AV (mm)	-10.4 (6.6)	-10.4 (8.4)	-11.3 (9.7)
SNB (°)	77.2 (4.0)	76.8 (4.0)	75.7 (4.4)
Basket. L (mm)	108.7 (6.2)	118.4 (9.0)	125.9 (10.3)
FH-MP (°)	30.9 (5.8)	31.9 (6.3)	32.6 (7.0)
ANB (°)	-0.5 (2.9)	-0.3 (3.7)	-1.9 (3.3)
Max basket. diff. (mm)	29.6 (3.9)	35.3 (7.4)	41.8 (7.0)
Wits value)mm)	-7.8 (3.2)	-6.4 (5.4)	-6.8 (5.8)
U6-AV (mm)	-37.7 (3.5)	-34.4 (4.1)	-33.5 (4.0)
U1-FH (°)	97.0 (9.3)	110.1 (8.7)	109.8 (6.9)
Overjet (mm)	-6.2 (3.0)	-1.9 (5.6)	-2.2 (6.5)
Overbite (mm)	4.2 (2.8)	2.5 (2.3)	1.8 (1.6)

Values of linear measurements are positive in the anterior direction. MP = maxillary protraction; A-PV = point A – posterior vertical reference line distance; A-AV = point A-anterior vertical reference line distance; Max L = maxilalry length; Pog AV = pogonion – anterior vertical reference line distance; Mand. L = mandibular length; FH-MP = Frankfurt – mandibular plane angle; Max. – basket. diff. = difference between maxillary and mandibular length; U6-AV = maxillary molar – anterior vertical reference line distance; U1-FH = upper incisor – Frankfurt horizontal plane angle.

Grading the evidence

The quality of evidence was graded as very low, due to the retrospective observational nature of the study (low evidence), the small sample size in both studies, and the mixed ethnic background of the sample in the Borzabadi-Farahani (2014). GRADE states that observational studies are graded as low quality of evidence by beginning. Due to imprecision (small sample size with no underlying power calculation), the quality of evidence was further downgraded by one level, from low to very low.

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out on the following scientific question and related PICO:

Will maxillary protraction reduce midfacial deficiency as compared to no treatment in cleft lip and palate patients?.

P: Cleft lip and palate patients;

I: Maxillary protraction;
C: No treatment;
O: Primary outcomes: reduction of midfacial deficiency, overjet, ANB angle, Wits appraisal, facial aesthetics. Secondary outcomes: Adverse effects, self-esteem.

Relevant outcome measurements
The working group considered a reduction in midfacial underdevelopment and an increase in overbite as critical outcome measures during decision-making. The working group considered the facial aesthetics, side effects of treatment and quality of life for decision-making important outcome measures.

The working group did not a priori define the aforementioned outcome measures, but used the variables and definitions used in the studies.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and September 24th, 2014. This search aimed to identify systematic reviews, randomized controlled trials (RCTs), ccts, and observational studies.

Studies included were systematic reviews, RCTs, controlled trials and observational studies that described at least one of the primary outcomes (reduction of midfacial deficiency, overjet, ANB angle, Wits appraisal) in patients with cleft lip and palate who underwent maxillary protraction. It was essential that the long term effects of the maxillary protraction (after maturity, defined as 18 years of age) were described in the study, ergo that a sufficiently lengthy follow-up was performed.

The initial search identified 371 references of which 48 were assessed full text.. Forty-six studies seemed to be relevant, but after examination of the full text did not answer the research question adequately, or did not present data on the effect size or association for the outcomes of interest with the required follow-up time.
Finally, two retrospective observational studies were included.

Reporting

Last reviewed: 09-01-2018 Last
authorized: 09-01-2018

For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html. https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Orthodontic treatment in patients with a CLA/P - Retention

Primary question

Which retention equipment is most effective in the long term in children with a (cheilognatho
) palatoCLA/P in maintaining the tooth position reached and the arch shape in the upper jaw?

Sub-question:
What length of retention is necessary to maintain the treatment outcome?

Recommendation

Use the same type of tooth retention as a patient without a CLA/P.

In addition, for the retention of the width of the upper arch on a patient with a lip, jaw and palate cleft, use a removable orthodontic retainer that is worn overnight for the rest of the patient's life.

Check the retainer at least once every two years.

Considerations

In a patient with CLA/P, two issues are important for the choice of retention after final orthodontic treatment. First, the tooth position should be retained. The retainer treatment is not different from that of a patient without a CLA/P. The second aspect to consider is the tendency of the transverse dimensions of the arch to relapse. This is particularly true in patients who have had surgery on the palatum, i.e. in patients with an operated cheilognathopalatoCLA/P and to a lesser extent in patients with an operated palatoCLA/P.

Animal studies have shown that the presence of scar tissue on the palatum contributes to the growth disturbance of the upper jaw as commonly seen in patients with CLA/P (Wijdeveld, 1991; von den Hoff, 2013; Semb and Shaw, 2013; Li, 2015). The surgical closure of the lip, on the other hand, has a very limited adverse effect on growth. Also, mature palatal scar tissue is still different from non-operated tissue: The scar tissue is less vascularized, less cell-rich, has no elastic fibers and shows an orientation of collagen fibers in the transverse direction. Also, the scar tissue is anchored to the palatinal bone, while for non-surgical tissue this is much less the case. In addition, the collagen fibers in the scar tissue are partly continuous with the collagen fibers of the periodontal ligament (Van de Water et al, 2013; Von den Hoff et al, 2013; Li et al, 2015). As a result, the palatinal scar tissue is probably partly responsible for the great tendency to relapse the transverse dimensions of the upper arch. The only research (Marcusson, 2004) that we were able to include in our literature research indeed shows that the archway of the above is narrowing in the long term, regardless of the retention method used. However, this research scores very low on the quality of the scientific evidence found.

Since the systematic literature study of retention after orthodontic treatment in CLA/P is not

scientific evidence of the procedures to be followed, the recommendations are therefore based on expert opinion. In addition to tooth retention, it is recommended to limit the tendency to transverse relapse of the upper dental arch by applying permanent overnight retention in the form of a removable retention device.

Substantiation Background

At the end of any orthodontic treatment, whether it concerns a patient with or without a CLA/P, the shape of the dental arch and the position of the dental elements must be retained by means of removable or fixed retainer. Without retention, the teeth tend to return completely or partially to their original position. Orthodontic retention can consist of fixed wires behind the upper and lower front, removable retainer or a combination of both. The retainer can remain in position for life (permanent retention) or for a limited period of time.

In patients with CLA/P, the functional conditions are different than in patients without CLA/P. There is scar tissue in the lip and on the palatum. Also, nasal patency may be disturbed, causing habitual breathing through the mouth and that the tongue may be lower in the oral cavity. Furthermore, there are often substantial dental rotations and a lack of dental elements before treatment. All of these factors affect the long-term results of treatment.

It is important to know which retention strategy in patients with an operated-on CLA/P leads to the most stable end result in the long-term with respect to tooth position, arc shape and occlusion. This concerns both the type of retention and the duration of the retention. In addition, the question of which type of retention is most acceptable to the patient and what the adverse effects may be.

Conclusions

Very low GRADE	There is evidence of very low quality that the maxillary arch dimensions are similar in unilateral cleft lip and palate patients, whether they undergo no retention of the upper arch or retention with a bonded twisted retainer or an onlay/fixed bridge. *Marcusson, 2004*

Summary of literature

Description of included study
One study was included in the literature summary, the prospective observational study of Marcussen, 2004. The purpose of this study was to evaluate the occlusion and maxillary dental arch dimensions in adults with repaired complete unilateral cleft lip and palate and to investigate patterns of change in early adulthood.

A total of 39 patients, all adults, were included in this study. These patients had undergone their primary surgery in the Cleft Centre of Linköping (Sweden) consisting of lip closure according to the Millard technique (at 3 months of age) and palatal closure according to the Wardill-Kilner technique (at 18 months of age). All

patients had received orthodontic treatment with fixed appliances by the cleft center orthodontists or elsewhere. The patients were then divided into three groups according to the type of retention in the upper arch: 1) no retention (n=15), 2) retention with a bonded twisted retainer (n=13), 3) an onlay or fixed bridge (n=11). Occlusion was evaluated according to a scoring system developed by Huddart and Bodenham. Dental casts were tasks at baseline (defined as 19 years of age) and at end of follow-up. The maxillary arch dimensions were measured digitally using a video imaging system with a magnification of 3x. Patients were followed for a mean of 5.6 years (range 0.9 – 9.6 years).

Results

Marcusson, 2004 reported that the occlusal score and the maxillary arch dimensions were reduced in all of the three groups, but there was no difference between the three groups, as shown below in Table 1.

Table 1. Difference (in mm) and P-values for maxillary arch dimensions between baseline and end of follow up for three different retention procedures

Measurement	No retention (n=15)		Bonded retainer (n=13)		Onlay/ fixed bridge (n=11)		p-values between groups	Total sample (n=39)		
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	p-value
Maxillary canine width	-0.7	0.9	-0.6	0.6	-0.5	0.8	>0.05	-0.6	0.8	<0,001
Maxillary second premolar width	-1.6	1.4	-1.7	1.6	-1.7	1.4	>0.05	-1.7	1.4	<0,001
Maxillary first molar width	-1.7	1.6	-1.1	1.3	-1.4	1.3	>0.05	-1.4	1.4	<0,001
Maxillary saggital length	-1.0	0.9	-0.6	0.8	-0.6	0.9	>0.05	-0.8	0.9	<0,001
Arch length cleft side	-1.5	1.3	-0.7	0.9	-0.9	0.7	>0.05	-1.1	1.1	<0,001
Arch length non-cleft side	-1.1	1.4	-1.0	1.2	-1.1	0.9	>0.05	-1.0	1.2	<0,001
Overjet	-0.2	0.6	-0.4	0.7	-0.2	1.2	>0.05	-0.3	0.8	<0.05
Overbite	-0.3	1.1	0.0	0.8	0.0	0.7	>0.05	-0.1	0.9	>0.05

Regarding the entire sample of 39 patients: There was a significant deterioration in the total cross bite score during the follow-up period and this was larger on the cleft than on the non-cleft side. There were no significant differences in the anterior scores. The transversal and sagittal maxillary arch dimensions decreased significantly during the follow-up interval, also as demonstrated in Table 1, regardless of the type of retention.

Grading the evidence

GRADE states that observational studies are graded as low quality of evidence by beginning. Due to imprecision (small sample size with no underlying power calculation), the quality of evidence was further downgraded by one level, from low to very low.

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out on the following scientific question and related PICO:

Will maxillary protraction reduce midfacial deficiency as compared to no treatment in cleft lip and palate patients?

P: Cleft lip and palate patients who have finished orthodontic treatment;
I: Orthodontic retention procedure A;
C: Orthodontic retention procedure B;
O: Maintaining/stabilizing teeth in corrected positions following orthodontic treatment or prevent relapse = Little's index, GOSLON Yardstick, cross bite score f.e. Huddart score, maxillary arch shape and arch width, duration of retention.

Relevant outcome measurements
The working group considered the measures for correct tooth position and jaw relationship of the jaw (Little's index, GOSLON Yardstick, cross bite score f.e. Huddart score, maxillary arch shape, arch width) critical outcome measures for decision making. The working group considered the retention period to be an important measure of outcome for decision-making.

The working group did not a priori define the aforementioned outcome measures, but used the variables and definitions used in the studies.

Search and study selection (methods)
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and September 24th, 2014. This search aimed to identify systematic reviews, randomized controlled trials (RCTs), ccts, and observational studies.

Studies included were systematic reviews, RCTs, controlled trials and observational studies that described at least one of the primary outcomes (Little's index, GOSLON Yardstick, cross bite score f.e. Huddart score, maxillary arch shape, arch width or duration of retention) in patients with cleft lip and palate who underwent retention. It was essential that the long term effects of retention (after maturity, defined as 18 years of age) were described in the study, ergo that a sufficiently lengthy follow-up was performed.

The initial search identified 178 references of which 24 were assessed full text.. Twenty three studies seemed to be relevant, but after examination of the full text did not answer the research question adequately, or did not present data on the effect size or association for the outcomes of interest with the required follow-up time. Finally, one prospective observational study was included.

Reporting

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Orthodontics: Le Fort I osteotomy versus distraction osteogenesis in CLA/P

Primary question

What considerations must be taken into account for forward displacement of the maxilla by using a classic Le Fort-I osteotomy or distraction osteogenesis in patients with a CLA/P?

Recommendation

Consider a classic LE Fort-1 in combination with a setback osteotomy of the mandibula in CLA/P patients with such a sagittal discrepancy between the upper and lower jaws that it can no longer be resolved by orthodontic therapy alone. Only consider a distraction osteogenesis in large sagittal discrepancies. Both treatments have specific advantages and disadvantages, which allows the choice to be determined per individual patient and per surgeon.

Considerations

The choice of a combined orthodontic-surgical treatment course in patients with a CLA/P should not be very different from that in non-CLA/P patients and is generally agreed on. The indication for orthogonal treatment is such a large sagittal (and sometimes transverse) dental and skeletal discrepancy between the maxilla, mandibula and the other parts of the face that it can no longer be resolved with orthodontic therapy alone and/or patients experience functional, aesthetic and/or psychosocial complaints.

In this module on osteotomies in patients with CLA/P, the question of which considerations play a role in the choice between a LF1 or a DOG of the maxilla was examined. In concrete terms, patients with a CLA/P usually have a large, reversed sagittal overbite and a corresponding hypoplasia of the maxilla, with sometimes also a transverse discrepancy. The goal of treatment is to restore skeletal discrepancy, improve facial aesthetics, achieve good occlusion and articulation, and increase patient quality of life. In particular, correction of, the reclining upper jaw so characteristic of CLA/P and hypoplasia of the middle face is essential from an aesthetic point of view.

The working group’s main question was which surgical technique is best and most predictable, the above goals can be achieved: with a LF1, whether or not in combination with a osteotomy of the mandibula and/or chin or a DOG of the maxilla. A major disadvantage of moving the maxilla forward is a possible deterioration of speech due to an increase in the velopharyngeal insufficiency. The working group was therefore keen to find out whether it is possible to predict when this problem will arise and whether it is a matter of which operating technique is used.

Although it seems obvious that a greater forward movement of the maxilla would be accompanied by a greater risk of the post-operative deterioration of the voice, no specific burden of proof can be found in the literature consulted. The level of speech before the osteotomy is also important here. If pre-existent velopharyngeal insufficiency is already present, a ventral maxilla displacement may have a more negative effect on this than if it is not. A

predictive value in size and number, however, is not available. Since a possible worsening of speech could be a major disadvantage of moving the maxilla forward, we considered it important to look at whether or not there will possibly be an emergence of velopharyngeal insufficiency after forward displacement of the maxilla in CLA/P patients. None of the studies we have included could answer this question. A study not included in this research mentioned more speech deterioration when there is preoperative borderline or evidenced velopharyngeal insufficiency (Witzel, 1995; Janulewicz, 2004). Another study correlates the degree of anterior displacement of the upper jaw with the risk of postoperative velopharyngeal insufficiency (VPI), in which patients with extreme preoperative retromaxillia in the DOG group show less VPI than LF1 patients (Kumar, 2006).

When looking at speech as an outcome measure in the studies included, no significant difference is found between LFI and DOG at the level of hypernasality, nasal air loss and velopharyngeal insufficiency. A possible explanation for this could be that the distance over which the maxilla is to be moved to Ventral is the same, whether an FVC or a DOC is being executed. The main difference is that this happens with a conventional FVC at once and with a DOG over a period of 2 to 3 weeks.

The next critical outcome measure considered is which of the 2 surgical interventions shows the most stable end result, in other words which gives the least relapse. This can be looked at on 3 levels: dentition (occlusion), bone and soft tissue. The systematic review of Kloukos (2016) stated that both interventions have a positive effect on soft tissue and especially the upper lip, but the differences between them are not statistically significant. The skeletal level relapse was measured in the studies on lateral X-ray skull profiles at 2 points: Subspinal A point and placed on a microscrew at the level of the mesial radix of the first molar in the upper jaw. Both the short-term (1 years) and long-term results (5 years) show that an LFI osteotomy shows a relapse to posterior and cranial. The maxilla in the DOG group is still moving postoperative to anterior and caudal. As the main explanation for the better stability of the DOG, it is postulated that the gradual displacement of the maxilla plays a role in this. The fact that the maxilla in a DOG still comes forward and down in the postoperative phase is attributed to the use of elastic bands that pull the maxilla in this direction. All measurements were made on LSPs and not on (CB)CTs. For occlusion as a measure of stability, 3 out of 25 patients in the LF1 group and 1 out of 22 in the DOG group eventually end up in Class III malocclusion. Based on this small difference in number, it can only be said that both techniques usually achieve good final occlusion. What is worth mentioning, but that is not really used in the Netherlands, is that no autologous bone graft (rib, or iliac crest) is reported in any of the studies examined simultaneously with the classic Le Fort-1 osteotomy to overcome the large ossal bridging and to achieve better ossification with less relapse.

In addition, the literature also does not mention the differences in the final chewing potential, an important objective of an orthogonal trajectory, between a LF1 and a DOG.

Since an orthogonal trajectory and forward displacement of the maxilla are intended to improve the sometimes stigmatizing profile in a patient with CLA/P, we wanted to include both aesthetics as well

as outcome. The Cochrane review writes about aesthetics based on the analysis of the X-ray skull profile. However, the working group is of the opinion that aesthetic change cannot be adequately measured with this medium.

The Cochrane review of Kloukos (2016) is based on one study group of 47 patients described in 6 articles. The small group of patients, together with the many methodological shortcomings in the study, result in a high overall bias risk and the overall quality of evidence is therefore low. Therefore, the review does not allow a clear answer to the question we have asked. Based on the literature consulted, therefore, no advice can be given about when to choose an LF1 and when to choose a DOG. However, we felt that we should make a statement about this in the recommendations below based on “expert opinion”. We have supported this expert opinion by the question and policy when to present an LF1 and when to present a DOG to MKA surgeons from the larger CLA/P teams in the Netherlands.
Since no significant differences between the LF1 and the DOG are found on almost all outcome measures, it seems appropriate to apply the DOG only if the distance to be crossed to the ventral can no longer be reached with an LFI alone, and a simultaneous setback of the mandibula for whatever reason is not desirable. For non-CLA/P patients, the maximum distance over which the maxilla can be moved to ventral is approximately 10 to 12 mm. In patients with CLA/P, this is generally less due to the presence of palatal scar tissue that has developed after closure of the palatum molle and durum.

When the ventral movement of the maxilla to be achieved with an LF1 or DOG is so large that this does not seem feasible, a combination with a set back of the mandibula can also be chosen. The disadvantage of this is, among other things, the risk of neuropraxia of the alveolar inferior nerve and a potential to luxorize or worsen obstructive airway problems. Of course, this intervention must fit in with the patient's profile planning.

Disadvantages of DOG in general are higher costs of the distractor and the fact that a second intervention is needed to remove the distractor. Patients also tend to experience more problems with a distractor related to post-operative pain and wound infections. It is also difficult to determine the right vector for the direction of distraction (Baas; 2015).
In addition, the direct postoperative post-treatment, both surgical (e.g. the use of intermaxillary fixation) and orthodontic, has been underexposed in the literature. However, the working group believes that this is important for achieving a good end result.

Of course, it is important to discuss and explain the considerations that determine the final choice of a LF1 or DOG with the patient and his or her parents.

Substantiation Background

In patients with cheilognathopalatoCLA/P or solitary palatoCLA/P, there is often a growth retardation (hypoplasia) of the maxilla in three dimensions. The underlying cause is an intrinsic growth deficiency in

combination with an effect on growth due to surgical interventions for closing the lip and especially the palatum at an early age. For correction by ventral traction by orthodontic equipment, refer to the module entitled "Orthodontic treatment in patients with CLA/P – ventral traction". If necessary, the growth retardation at the end of the growth period can be corrected with a combined surgical-orthodontic treatment. Prior to the surgical correction, the upper and lower dental arches are orthodontically aligned, where after the sagittal skeletal discrepancy and possibly the vertical and transverse discrepancy are corrected by osteotomy of the maxilla, whether or not in combination with osteotomy of the lower jaw and chin.

In patients with a CLA/P, this must wait until the patient is fully grown and the classic LE Fort-I osteotomy (LF1) only occurs from the age of 17 to 18, like in patients without a CLA/P with a maxillary hypoplasia. In patients without CLA/P, treatment, especially in mandibular hypoplasia and a horizontal growth pattern, is often performed before, even if patients are not yet fully grown.

In order to move the maxilla to ventral, the LF1 is often chosen, with or without a sagittal fission osteotomy of the lower jaw with dorsal displacement. If there is also a transverse and/or vertical discrepancy, the LF1 can be performed in multiple segments or a surgical or non-surgical widening. This module will not cover this issue. However, there is also room for distraction osteogenesis (DOG) of the maxilla especially when there is a large sagittal discrepancy which cannot be solved with a LF1. This procedure can be combined with a BSSO if desired. This module will not cover this issue.

In this module of the directive, the working group tries to formulate an answer to the initial question in which situation an FVC osteotomy is preferred and when DOG is a good choice.

Conclusions

Very low GRADE	We found very low quality evidence that le Fort-I osteotomy, compared to distraction osteogenesis, is not associated with differences in speech, nasal emission, and velopharyngeal function in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2010b)*

Very low GRADE	We found very low quality evidence that the classical le Fort-I osteotomy, compared to distraction osteogenesis, is associated with more skeletal relapse and a lower skeletal stability in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2010a)*

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of classical le Fort-I osteotomy, compared to distraction osteogenesis, on type and amount of revisional or corrective surgeries in patients with a cleft lip and palate .

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of classical le Fort-I osteotomy, compared to distraction osteogenesis, on chewing function in patients with a cleft lip and palate.

- GRADE	We found insufficient evidence to formulate a conclusion on the effect of classical le Fort-I osteotomy, compared to distraction osteogenesis, on malocclusion in patients with a cleft lip and palate.

Very low GRADE	We found very low quality evidence that the classical le Fort-I osteotomy, compared to distraction osteogenesis, is associated with anteroposterior postoperative differences in cephalometric values for maxillofacial morphology in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua,*

Very low GRADE	We found very low quality evidence that the classical le Fort-I osteotomy, compared to distraction osteogenesis, is associated with no differences in patient reported outcome (pros) in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). *Sources (Chua, 2012a)*

Summary of literature

Study description

One study, a systematic review of Kloukos (2016), was included in this literature summary. Kloukos (2016) aimed to investigate the short- and 5 years effects of maxillary distraction osteogenesis (DOG) compared to LE-Fort-I osteotomy (LF1), in patients with a complete unilateral cleft lip and palate, or a complete bilateral cleft lip and palate (involving the alveolar process). Primary outcome measures were: 1) changes in midfacial and/or transversal soft and hard tissue (assessed by superimposing lateral cephalometric radiography and/or photographic archives, when applicable. Transversal maxillary changes were assessed with anteroposterior cephalometric radiography or digital cast models of the occlusion); 2) relapse and/or change after treatment (assessed with lateral cephalographs tasks at different postoperative times) and 3) perceptual speech assessment (id est articulation, resonance (hypernasality and hyponasality) and nasal emission using f.e. video, conducted by a professional speech-language therapist.) Secondary outcome measures were: 1. instrumental assessment of velopharyngeal function (nasoendoscopy or videonasopharyngoscopy or videofluoroscopy); 2)

patient-reported outcomes (assessment of self-esteem and psychological adjustment by validated and internationally accepted questionnaires) and 3) adverse effects of clinical morbidities of the surgical procedure (for example mucosal infection, sinusitis, transection of vessels) (Kloukos, 2016).

In the systematic review RCTs investigating the short- and long-term effects of LF1 versus DOG in non-syndromic cleft patients aged 15 years and older were included. Five databases were searched until February 2016 (Kloukos, 2016). Initial 416 studies were included, but 400 studies were excluded based on title and/or abstract analysis. Sixteen articles were evaluated on full-text, ten studies were eliminated, six remained (Cheung, 2006a; Chanchareonsook, 2007; Chua,2010a; Chua,2010b; Chua,2012a; Chua, 2012b). The six articles were all based on one randomized controlled trial performed between 2002 and 2008 at the University of Hong Kong. Not all the publications reported all the outcomes of all the participants (Kloukos, 2016).

The six publications describe the characteristics of 47 participants, which needed maxillary advancement of 4 mm to 10 mm (Kloukos, 2016). The included patients underwent a LF1 or DOG and were between 13 and 45 years of age. Studies about participants with a syndromic, atypical, and/or unclear type of cleft and palate were excluded. The study has several methodological limitations: a small sample size, and a high risk of several types of bias (selection, performance, detection, attrition, reporting and probable other types of bias) (Kloukos, 2016).

Both treatments produce significant soft tissue improvements (Kloukos, 2016). DOG tended to give more stable long-term results. Speech and velopharyngeal status was comparable in both groups. DOG seems to reduce the self-esteem of the participants, until the distractors were removed, at three months postoperatively, but two years after surgery this surgical procedure improves self-esteem (Kloukos, 2016).

Results

Speech and velopharyngeal function

Two publications were included in the systematic review which assessed the effect of LF1 versus DOG on speech and velopharyngeal function. Data from 22 out of 47 participants were available (Chanchareonsook, 2007; Chua, 2010b). Only the most recent paper with the longest follow-up time was used in the analysis, because data of the two studies overlapped (Chua, 2010b). The mean advancement in both the LF1 and the DOG-group was 6.5mm. No statistical significant difference, between LF1 versus DOG, was found in hypernasality (RR 9.0, 95% CI (0.54, 149.5)), nasal emission (RR 0.33, 95% CI (0,015, 7.39)), and velopharyngeal
function (RR 0.78, 95% (CI 0.40, 1.53)) at 17 months postoperatively (Chua, 2010b).

Evidentiary value of literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example sample size calculation was only performed for the outcome skeletal relapse).

Skeletal relapse

Two publications were included in the systematic review which examined relapse of the maxilla. One article examined short-term relapse (one year postoperatively) in 29 participants, another article assessed long-term relapse (five years postoperatively) in 47 participants. Long-term (five years postoperative) relapse is not only determined by relapse, but might also be influenced by skeletal growth. Therefore, the guideline working group decided to describe long-term relapse as change after treatment. The maxillary relapse and change after treatment was examined using series of lateral cephalograms. Data of the two studies overlapped, therefore only the study of Chua (2010a), which investigated the long-term effects was used. In the study of Chua (2010a) 47 participants were included, 25 participants underwent LF1 and 22 participants DOG. Long-term data were available of only 16 participants. In the patients, which underwent a LF1, the A-point (subspinal) and P-point (a microscrew placed at the mesial root of the upper first molar) showed horizontal relapse with 2.53 mm and 2.45 mm, respectively five years postoperatively (Chua, 2010a). In the DOG-group the A-point and P-point moved anterior with 2.27 mm and 2.51 mm respectively five years postoperatively (mean difference A- point: -4.8 mm, 95% (CI -9.19, -0.41)). Moreover, it was mentioned in the included systematic review that five years after the surgical intervention, 3 of the 25 participants in the LF1-group, and 1 of the 22 participants in the DOG-group, changed into a Class III occlusion, despite orthodontic intervention and surgical repositioning (Kloukos, 2016).

Evidentiary value of literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example wide confidence interval).

Revisional or corrective surgery

Differences in revisional surgery (for example pharyngoplasty), between participants in the LF1-group and the DOG-group, were not assessed in the included systematic review.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found investigating differences in revisional surgery, between participants in the LF1-group and the DOG-group.

Chewing function

Differences in chewing function, between participants in the LF1-group and the DOG-group, were not assessed in the included systematic review.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found, investigating differences in chewing function, between participants in the LF1-group and the DOG-group.

Malocclusion

Differences in the prevalence of malocclusion, between participants in the LF1-group versus the DOG-group, were not assessed in the included systematic review.

Evidentiary value of literature

Grading the evidence was not possible, because no articles were found, investigating differences in occlusion, between participants in the LF1-group and the DOG-group.

Alterations in soft and hard tissues

One article was included in the systematic review which investigated alterations in soft and hard tissues, including 39 participants (Chua, 2012b). The alterations were measured through the change in position of various cephalometric landmarks horizontally (x) and vertically (y). The LF1 group, compared to the DOG- group, indicated less maxillary advancement, described as the advancement of Subspinal A-point: (MDS) or -
5.63 mm (P= 0,003) six months postoperatively, -5.27 mm (P= 0,005) one year after the operation and -4.40 mm (95% CI -8.56, -0.24) two years postoperatively. The LF1 group, compared to the DOG-group, indicated non-significant horizontal changes in the soft tissues such as pronasale (MD -0.94 mm, P= 0.74), subnasal (MD 1.53 mm, P= 0.33) and stomion superius (MD -4.20 mm, P= 0.12). The LF1 group, compared to the DOG group, indicated statistical significant changes in labral superius after two years of follow-up (MD 3.42 mm, P=0,023). Changes tended to be greater in the distraction-osteogenesis group, but no firm evidence indicated soft tissue differences between the two groups (Chua, 2012b).

Evidentiary value of literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example sample size calculation was only performed for one outcome measure).

Patient reported outcomes (pros)

Patient reported outcome (pros) were measured until 2 years after surgery (Chua, 2012a). There was no difference between the LF1-group and DOG-group in terms of Social Avoidance and Distress Scale (SADS) at any time point. To measure self-esteem the Cultural-Free Self-Esteem Inventory (CFSEI) was used. There was also no difference between the groups in general self-esteem after 12 and 24 months, however patients who underwent DOG had a significant lower social self-esteem in the first three months postoperatively (P= 0,023). After 6 months there was no significant difference in self-esteem between the groups (P=0,896). Satisfaction with life was measured with the Satisfaction With Life-Scale (SWLS). After two years postoperatively, patients in the LF1 group were less satisfied with life, compared to patients in the DOG group (MD -2.95, 95%CI -5.76,
-0.14, P= 0,001) (Chua, 2012a).

Evidentiary value of literature

Grading the evidence started at a level of high evidence, because the used data was derived from a RCT. Downgrading with four levels was, however, necessary as there were limitations in study design (for example selection bias, attrition bias), there was indirect evidence (for example narrow range of participants with a specific ethnicity and specific disease characteristics used) and imprecision (for example sample size calculation was only performed for one outcome measure).

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out on the following question:

What is the effect of a classic Le Fort-I osteotomy (LF1), compared to distraction osteogenesis (DOG), on speech development, relapse, revisional surgery, chewing function, malocclusion and postoperative status and bone-to-soft tissue ratio in patients with a CLA/P?

P: Patients with a CLA/P;
I: Classic LE Fort-I osteotomy (LF1);
C: Distraction osteogenesis of the upper jaw (DOG);
O: Speech (e.g. velopharyngeal insufficiency/rhinolalia aperta), relapse, revision surgery (e.g. speech enhancing surgery), chewing function, malocclusion, postoperative bone and soft tissue ratio and patient reported outcomes (pros).

Relevant outcome measurements
The working group considered speech (e.g. velopharyngeal dysfunction/rhinolalia aperta), relapse, revision surgery (e.g. pharyngeal plasty), chewing function and malocclusion critical outcome measures for decision-making; and stability and aesthetics important outcome measures for decision-making. The working group did not define the aforementioned outcome measures a priori, but used the definitions used in the studies. The working group did not define any clinically (patient) relevant differences.

Search & Select (Method)
A systematic Cochrane review was used to elaborate the research question. The topic of that systematic review is comparable with the research question (Kloukos, 2016).

Additionally, a systematic search was performed, with relevant search terms, in the databases of Medline (though OVID), and Embase (though Embase.com) between 1948 and May 2017. The search aimed to check the sensitivity and specificity of the search performed for the Cochrane systematic review, and to identify systematic reviews, randomized controlled trials (RCTs) and observational studies published after the last search date as reported in the Cochrane systematic review. The search strategy is described under the tab “Accountability”.

Studies which investigated the effectiveness of LF1, compared to the DOG, in patients with a cleft lip and palate were selected. The initial search identified 421 references, which indicated that the search of the systematic review was sensitive and specific. Four studies, published after the publication date of the systematic review, were identified. All these studies were excluded after reading title and abstract. Reasons for exclusion are described in the exclusion table.

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html. https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Nasal correction in patients with a CLA/P

Primary question

What are the indications for nose corrections at an early age in children with a (cheilognatho) palatoCLA/P?

Recommendation

In the primary lip closure, pay attention to the primary correction of the nasal wing and caudal septum position and columella of the nose.

Preferably postpone secondary surgery on the nose at CLA/P until the midface growth is complete and any orthogonal surgery is completed to reduce the total number of interventions.

Considerations

It is important to realize that many publications on early nose corrections in children with CLA/P only describe what the author did to the nose during the procedure, without an adequate comparison and without an adequate follow-up.[1] Several publications indicate that a primary nose correction can improve the shape, but the follow-up is often too short. It is also indicated that secondary nose corrections will still be needed later.[2] There is limited comparative research, unfortunately not followed up until the age of 18, but often only a few months to a few years.[3] It is regularly claimed that an external nose and/or septum correction can be performed at an early age, but often the justification and sufficient follow-up are lacking.[4]

There are also publications that indicate that early nasal surgery may indicate growth slowing of septal growth and nasal outgrowth forward. There is no likelihood of catching up. (Kobus, 1978; Krupp, 1990; McComb, 1990; Roberts-Harry, 1996; Rullo, 2009; Takato, 1990, Wray, 1976). Some publications indicate that secondary nasal surgery can improve the shape of the nose, but it is still different from the non-CLA/P population (Meazzini, 2010; Okawachi, 2011). During the lip closure, the nose wing is usually moved and the columella adjusted, but often no real rhinoplasty is performed with adjustment of the os nasal, lower and upper lateral cartilage bones and the complete nasal septum (Ahuja, 2001; Kim, 2004). NASO-alveolar molding would make primary lip-nose closure easier, but there is no comparative study (with versus without naso-alveolar molding) evaluating the effect on the nose (Van der Heijden, 2013).
It is good to keep realizing that the bone grafting procedure has an effect on the nose, as well as a LeFort 1 osteotomy (Agarwal, 2012; Heliovaara, 2001; Takato, 1994; Wu, 2013). It is therefore prudent to perform the final nasal correction only after stabilization of Le-Fort osteotomy after completing any orthogonal trajectory. (WU, 2010; expert opinion).

The working group concludes that the potential disadvantages of early nasal surgery (growth retardation, more difficult final surgery in adult age due to scar tissue) mentioned in the literature are not compensated by proven benefits. There is lack of evidence that the nasal shape becomes normal or improves a lot after early nose correction

so that this produces has a positive impact on the psychosocial well-being of the patient. So there are no psychosocial arguments that justify early nose surgery.

The working group concludes that if nasal massage disorders occur at an early age, a concha reduction may be considered to improve functional complaints (Bhandarkar 2010).

If the patient or their parents express a wish for early nasal surgery, this question should be considered seriously. It should be discussed that according to the literature, early nasal surgery does not lead to a normal nasal shape and that surgery is often still needed at adult age. Also, there is no evidence that early nose surgery eliminates possible psychological concerns. It is advisable to involve a psychologist or a behavioral in the decision-making process in order to appreciate the desire to improve the appearance. If necessary, psychosocial treatment can also be initiated. Also remember to mention the disadvantages of surgery such as the risk of scars and the chance that the result will not last.

[1] Angelos, 2012; Ayhan, 2006; Bagatain, 2000; Balaji, 2003; Black, 1984; Carlino, 2012; Chaithanyaa, 2011; Chang, 2011; Chen, 1996; Cho, 1998;

Cho, 2001; CH0, 2002; CHO, 2012; Duskova, 2006_1; Duskova, 2006_2; Foda, 2005; Fujimoto, 2011; Garfinkle, 2011; Gubic, 1989; Gubic, 1998_1;

Slope, 2010; Huempfner-Hierl, 2009; Jeong, 2012; Karimi, 2012; Kim, 2008; Koh, 2006; Lee, 2011; Li, 2006; Marsh, 1990; McComb, 2009; McDaniel,

2013; Millard, 2000; Mootemri, 2013; Morselli, 2000; Nakajima, 2003; Nakajima, 1998_1; Nakajima, 1998_2Nakamura, 2010; Nakamura, 2011; Nolst,

2002; Offert, 2013; Orticochea, 1975; Pawar, 2014; Peled, 2003; Pitak-Arnknop, 2011_1; Prasetyono, 2014; Rettinger, 2002; Romo, 2003_1; Romo,

2003_2; Sandor, 2006; Sommerlad, 2006; STAL, 2000; Stenstrom, 1977; Tzvetkov, 2002; Uchida, 1994; Van der Meulen, 1992; Wang, 2007; Wang,

2010; Yan, 2011; Yonehare, 2008

[2] Agarwal, 1998; Ahuja, 2002; Ahuja, 2006; Anasstassov, 1998; Anderl, 2008; Armstrong, 1997; Borsky, 2007; Briggs, 1980; Brussels, 1999; Byrd,

2000; Chen, 1992; Chowchuen, 2011; Coghlan, 1996; Cronin, 2004; Cutting, 1998; Fontana, 1998; Gubic, 1998_2; Haddock, 2012; Hemprich, 2006;

Hood, 2003; Hrivnakova, 1987; Kernahan, 1980; Liou, 2004; Lo, 2006; McComb, 1985; McComb, 1986; McComb, 1994;

McComb, 1996; McComb, 2009; Mchaik, 2006; Millard, 1998_1; Millard, 1998_2, 2005; Mulliken, 2001_1; Mulliken,

2001_2; Nakamura, 2009; Numa, 2006; Onizuka, 1999; Ozcan, 1989; Pigott, 1985; Pitak-Arnknop, 2011_2; Solomons, 1996;

Salyer, 1986; Shih, 2002; Singh, 2007; Sugihara, 1993; Sulaiman, 2013;

Sykes, 2001; Tajima, 1997; Tan, 1993; tan, 2007; Thomas, 2009; Trier, 1985; Trott, 1993; Velazquez, 1975; Xu, 2009_1; Xu, 2009_2

[3] Ayoub, 2011; Brussels, 1999; Byrne, 2014; Chang, 2010; Garri, 2005; Horswell, 1995; Kohout, 1998; Lu, 2012; Marimuthu, 2013; Meazzini, 2010;

Reddy, 2013; Roberts-Harry, 1991; Roberts-Harry, 1996; Wakami, 2011; Wong, 2002

[4] Boo-Chai, 1987; Cheon, 2010; Cho, 2007; Cohen, 2009; Cutting, 1996; Edgerton, 1978; Flores, 2009; GoslaReddy, 2011;

Jackson, 2005;

Janiszewska-Olsowska, 2013; Jung, 2012; Kim, 2004; Lawrence, 2012; Masuoka, 2012; Matsuya, 2003; Morselli, 2012; Omori, 2003; Ortiz-Monasterio,

1981; Pause, 2013; Pitak-Arnknop, 2012; Rottgers, 2010; Salyer, 1992; Smolka, 2008; Thomas, 2000; Thomson, 1985

Background of the Substantiation

In the case of a lip CLA/P, the nose is always affected to a greater or lesser extent on embryological grounds. On the affected side, the nose wing is pulled laterally, making the nose tip less prominent with a displacement of the columella to the unaffected side. With a double-sided lip cleft, the condition leads to a short columella. Functional problems in the nasal passage may also arise due to a skew nasal septum. Adjustments to the nose are already made at the lip closure,

secondary corrections can be made later. Early correction leads to earlier correction of the abnormality, but may cause growth disturbances of the nose. The risk of growth disorders is particularly present if the septum is worked on at an early age, as the anterior septum contains an important growth center. It is therefore important to know which treatment strategy leads to the best (end) result.

Conclusions

Not applicable.

Summary of literature

Study characterics
No studies were identified during the literature search that answered the research question directly. However, two studies were found that had an indirect relation to the research question. Mccomb 1995 is an observational study that describes the long term results (18 years) of a primary rhinoplasty during cleft lip correction surgery (n=10) versus another (not further described) type of rhinoplasty (n=20) and healthy controls (n=23). Facial photographs of the study subjects were examined using a software program, and the degree of facial symmetry was determined. The following features were studied: In the anteroposterioir view: vertical sloping of the alar and the lower lip asymmetry; in the inferior (basal) view: The overall nasal outline, the upper nasal perimeter and the nostrils. Also the total amount of symmetry in all these features was determined.

Mccomb (2009) describes a case-series of 10 patients that are being evaluated 18 years after an open-tip rhinoplasty, performed simultaneously with a cleft lip correction surgery. One patient was lost to follow-up at the age of 14 years, thus these results are shown up to that age.

Results
Mccomb (1995) describes that the healthy controls had a significantly more symmetrical face compared to the cleft palate patients. There was no significant difference in facial symmetry between the cleft palate patients who underwent a primary cleft nose correction compared to that underwent a different type of rhinoplasty. Furthermore the facial symmetry of the cleft lip patients was compared at the age of 10 and 18 years, and no significant difference was found.

Mccomb (2009) reports in a case-series of 10 patients who underwent an open tip primary rhinoplasty during cleft palate surgery, that the nasal development of these patients is overall satisfactory. There is no interference with growth and the operative scar is barely visible.

Grading the evidence
It is not possible to grade this evidence, since the research question cannot be answered directly with the available literature.

Search and select

In order to answer the initial question, a systematic literature analysis was carried out based on the following PICO:

P: At least a cleft lip CLA/P;
I: Nasal correction (both primary and secondary) at age <18 years;
C: Nasal correction (both primary and secondary) at age > 18 years; **O:** Nose shape, functioning of the nasal passage.

Relevant outcome measurements
The working group considered the shape of the nose and functioning of the nose passage critical outcome measures for decision-making.

Search and selection
A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and March 12, 2014. This search was aimed to identify systematic reviews, RCTs, ccts, and observational studies. Detailed search characteristics are shown in the “underpinning”.

Studies that investigated patients with cleft lip and palate were selected if they compared rhinoplasty performed in patients below the age of 18 years with rhinoplasty performed in patients older than 18 years. It was essential that the long term effects of the rhinopolasty (after maturity, defined as 18 years) were described in the study. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: cosmetic appeal of nose shape and functional nasal passage.
The initial search identified 369 references of which 14 were assessed on full text.. Twelve studies, all with a non-randomized observational study design, seemed to be relevant but did not present data on the effect size or association for the outcomes of interest with the required follow-up time. Finally, two studies were included, although they did not answer the research question directly. No evidence tables and risk of bias assessments could be performed of these observational studies without a control group, although due to their design they were deemed automatically as very low quality of evidence.

Accountability

Last reviewed: 09-01-2018 Last authorized : 09-01-2018

For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html. https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Psychosocial care of patients with a CLA/P

Primary question

What is the effectiveness of psychosocial guidance from a multidisciplinary team for children with a (cheilognatho) palatoCLA/P and their parents?

- What are the best moments in the child's development for psychosocial counseling?

Recommendation

Screen the child with CLA/P and parents for psychosocial problems, after birth, at the age of 2 to 3 years, 5 years, 10 to 11 years and 17 years.

In this contact, screen child factors (well-being, possible learning problems, fear of medical interventions and acceptance problems) and family/parent factors (acceptance problems, mourning and education style).

Use the same validated tool (SDQ, GVL, parent and/or child conversation) in addition to calls within all the CLA/P teams.

Provide parents and child with further diagnosis or treatment based on the results of the screening if necessary.

Within the school team, appoint a post-graduate behavioral expert (health care psychologist or general remedial teacher and social worker, for the less complex problems) to diagnose psychosocial problems of the child and family and for the treatment of complex psychosocial problems.

Considerations

Diagnosis of psychosocial problems
Although parents in the focus group have indicated that they need psychosocial support for themselves and their child, no evidence has been found in the literature for specific psychosocial problems in children with an isolated CLA/P, when the whole group is compared to children without a CLA/P (Hunt, 2005; Feragen, 2007; Hoek, 2009). There are children with psychosocial problems within the total group of children with an isolated CLA/P, but there are no specific child characteristics (such as type of CLA/P, gender, age, dissatisfaction with appearance, self-image, cognitive development), which are directly related to the psychosocial well-being of the child. We know that within the group of children with isolated CLA/P there are children who develop psycho-social problems, it is only impossible to predict beforehand which children these will be. (Hunt, 2007; Feragen, 2009; Feragen, 2014).

It should be noted that the studies vary widely in research methodology, size of the

group, age of the study population, research resources used and the psychological constructs measured. More specifically, the article by Hunt (2005) notes that there is a tendency in literature to describe 'psychosocial functioning' in general. As a result, specific problems these children may have (such as acceptance, behavior, learning problems, self-image, satisfaction with appearance, bullying). As a result, the results of the studies are poorly generalizable and not comparable.

Clinical experience has shown that for parents, having a child with a CLA/P often leads to different emotions and reactions that can overwhelm parents. Feelings of disappointment about the abnormality are often difficult to handle. After all, as parents, you should be happy with your baby. You should not reject your child and be angry with it (for example, because you feel hurt). In addition, the reactions of family, friends and others to the abnormality can be very different and sometimes confusing.

The literature shows that the consequences of having a child with a congenital defect such as a CLA/P for a family are greater when the child is young and there are additional medical problems (Baker et al, 2008). In addition, family variables can influence the psychosocial development of the child. This includes demographic variables (such as socio-economic status). Also the educational skills (Murray et al, 2010), the level of parental stress (Endriga et al, 2003) and the mother-child interaction (Colett et al, 2009, Speltz et al, 2000) are listed as risk variables for the development of social-emotional problems, reading problems, language problems and lower cognitive potential in children with CLA/P.

No scientific studies are available about a possible increased risk of psychosocial problems due to the presence of a CLA/P in children. Therefore, no child factors have been identified, based on which you can predict which children are at an increased risk of developing psychosocial problems. Some individual parent factors (e.g. acceptance, disappointment, mourning) appear to be clearly contributing.

Because children with a CLA/P are examined and treated in a multidisciplinary CLA/P team and parents in the focus group have indicated that they would like to have all diagnosis and treatment integrated, it is desirable to include psychosocial diagnosis and treatment related to the CLA/P as standard in CLA/P care. A commonly used means of early detection of psychosocial problems in children and/or parents is a screening at fixed moments for aspects that can play a role with CLA/P in children and/or parents such as social emotional development, fear of medical treatment, problems with appearance and acceptance. It is precisely because it is not easy to predict in advance whether child factors and family/parent factors will lead to protection or hinder psychosocial development, it is advisable to perform a basic screening on all children with a CLA/P. Given the nature of the screening (a complex mix of protective and limiting child and family/parent factors), this is part of the duties of a post-graduate behavioral expert (health care psychologist or general educational expert). More specifically, the advice is to examine the following aspects of psychosocial development with regard to child factors and family/parent factors within this screening.

Diagnosis of child factors

Well-being

The literature shows that there is evidence that the sense of well-being of some children with a CLA/P is less than that of peers. This can be reflected in emotional, behavioral, and interaction problems, including problems in friendship relationships and being bullied (Hunt, 2004). Regularly check in with children and pay attention to what they experience in conversations with other children, because the literature shows that parents can have a different experience of the well-being and possible psychosocial problems of the child than the child itself, it is important to ask the parents about this on a regular basis. This is possible from a young age. It is recommended that a child is specifically asked if he/she is being bullied (Hunt, 2007), about social skills and the sense of self-esteem (Feragen et al, 2009).

In addition to the discussions with the child and the parents, we recommend using a validated tool to identify any psychosocial problems with the child. Both in international literature and psychodiagnosis, the SDQ (Strength and Difficulties Questionnaire, edited for the Netherlands by Treffers et al, 2000) is used as a measuring instrument for the diagnosis of psychosocial problems. The SDQ is an internationally validated screening list for children aged 3-17 years. This questionnaire can be completed by parents, teachers and the child (from 11 years). The list screens for emotional factors, behavioral problems, hyperactivity/lack of attention, problems with peers and pro-social behavior. This questionnaire will allow a decision to be made as to whether further investigation is indicated. The collection takes 5 to 10 minutes. The advice of the working group is to include this instrument as standard in the research protocol of the CLA/P teams because this (in addition to conversations) is a validated tool to identify psychosocial problems. Moreover, if all the precision teams use the same tool, it is possible to carry out broad scientific research on this. The standard execution and analysis of this screening tool as a complement to the conversation will take the behavioral expert about 10 minutes.

If screening with the child and/or parents indicates the presence of psychosocial problems likely to be related to the CLA/P or medical treatment thereof, further psychological examination within the CLA/P team is indicated. Within this more extensive diagnosis, especially in young children, play therapy may be an important tool (Murray et al, 2010).

Intelligence/cognition/learning

There is some evidence that some of the children with an isolated CLA/P could develop learning problems, especially reading and language problems (Hoek et al, 2009; Roberts, 2012; Wehby, 2014). Despite the suggestion in foreign literature to do intensive diagnostics within the CLA/P teams, the working group sees no reason to do this within the Dutch education system. The diagnosis of learning problems in Dutch education is guaranteed. However, it is advisable to inquire about school performance within the discussions. If this reveals details that have not been investigated within the regular educational structure, further research is indicated. This is also the case when there are doubts about the overall development (for example, a below average language comprehension) from the multidisciplinary team. This diagnosis can often take place within the regular educational structures unless a relationship is expected between the education problem and the

CLA/P and therefore specific knowledge from the CLA/P team is required. This is the case, for example, in children with CLA/P and multiple birth defects. The literature shows that this group scores lower on development tests as a group (Swanenburg de Veye, 2003). For this reason, it is important to follow the development of this group of children closely and to schedule repeat examinations from the CLA/P teams.

Diagnosis of family/parent factors

In addition to child factors, family/parent factors that are important to identify are also mentioned in the literature. The interaction between parents and child is an important factor in this. There are children with a CLA/P, where the parent-child interaction has been disturbed. These children are at increased risk of developing less favorably. (Hentges, 2011). The working group also considers it important to include factors such as parental stress, parents' educational skills and the acceptance of the CLA/P (e.g. possible grief therapy of not having a 'perfect' child) in the discussions, partly based on the clinical experience of parents in the focus group. In clinical practice, it is found that these variables can affect the education and thus the psychosocial development of children with a CLA/P.

With regard to the family/parent variables, the working group recommends using a validated screening tool in addition to calls. The Family Questionnaire (GVL, Van der Ploeg & Scholte, 2008) is an appropriate questionnaire for the identification of family factors. The GVL is a questionnaire that assesses the quality of family and educational conditions in children aged 4-18 years. The questionnaire can be completed by the child's parents or educators. The list screens for responsiveness (educational relationship), communication, organization, partnership and social network. The collection takes 30 minutes. The working group recommends that this tool be included as a standard in the research protocol of the CLA/P teams as it is a validated tool to identify family factors in addition to discussions. Moreover, if all the CLA/P teams use the same instrument, it is possible to conduct broad scientific research. The standard execution and extensive interpretation of this screening tool as a supplement to the conversation will take the behavioral expert about 15 minutes.

If the screening shows evidence of influential family/parent factors, further diagnosis from the CLA/P team is indicated. Within this diagnosis, following the request for help from parents and child, video recordings of their interaction should be used, as well as play observation there the interaction between parent and child can also be observed (Collett, and Speltz, 2006).

In summary, the advice to the CLA/P teams is to screen children with CLA/P for child factors as well as for family/parent factors through discussions and standardized instruments. When talking to parents and/or child, particular attention should be paid to problems related to the CLA/P and its medical treatment. No ideal ages have been identified in the literature for this screening to take place. However, some suggestions are made, for example at important transition periods. Based on the information from the literature, clinical experience and experiences of parents in the focus group, we recommend the following screening moments, sometimes only with parents and sometimes also with the child.

Basic diagnosis (screening) psychosocial problems

First weeks after birth	
Informant:	parents
Topics:	all family factors
Format:	conversation
Between the age of 2 and 3 years	
Informant:	parents and child
Topics:	psychosocial child factors and family factors
Format:	conversation with parents and observation of the child, interaction with parents
5 years*	
Informant:	parents
Topics:	psychosocial child factors and family factors
Format:	Interview and complete GVL and SDQ
10 to 11 years**	
Informant:	parents and child
Topics:	psychosocial child factors and family factors
Format:	Conversation with parents, conversation with child and fill in GVL and SDQ, conversation with parents, conversation with child
17 years	
Informant:	child
Topics:	child factors and discuss possible hereditary problems
Format:	conversation

* in the year before the child goes to group 3

** Group 7/8 of elementary school

This basic diagnosis for the identification of psychosocial problems will on average take 5 hours per child per treatment course and must be carried out under the final responsibility of a postgraduate trained behavioral expert. This calculation does not include any additional diagnostics that may be necessary.

Treatment of psychosocial problems

The literature gives advice about possible effective treatments or treatment goals. For children, it is recommended to start SOVA training courses (Collett and Speltz, 2006), cognitive behavioral therapy (Norman, 2014) or therapy aimed at teaching alternative coping strategies (Baker et al, 2008) where appropriate. It is recommended that parents go for grief and acceptance counseling, learn coping strategies (Endriga et al, 2003), and that parents' fears and concerns about their child and the future are discussed (Pelchat et al, 2004).

Based on clinical experience and recommendations from parents in the focus group, the working group concludes that parents and children should preferably be treated by specialized caregivers. The above treatment methods are performed in the Netherlands by therapists with different backgrounds. Depending on the complexity of the psychosocial problems and the need for help from parents, this can take place within the CLA/P team (by social worker, gz-psychologist or general educational expert) or in the periphery. It is possible to have treatment in the periphery with supervision from the CLA/P team. In addition to treatment, contact with other parents of children with a CLA/P can also be comforting. It is therefore desirable to inform patients at an early stage about existing patient organizations (such as the BOSK) and the possibilities they offer to connect with other parents and children online and offline.

If the diagnosis shows that there is a complex psychosocial problem, treatment by, or under the ultimate responsibility of, a post-graduate behavioral expert is indicated. Mild psychosocial problems can be treated by an HBO-trained therapist.

Summary and conclusions

Scientific literature does not conclusively conclude whether or not children with CLA/P have an increased risk of psychosocial problems (and what type of problems specifically); nor is it proven whether psychosocial guidance could help in this.

Due to a lack of scientific evidence, it is not possible to make a clear statement about a possible increased risk of psychosocial problems due to the presence of a CLA/P in children. Also, scientific literature does not provide sufficient leads to make a statement about the effectiveness of psychosocial counseling on the psychosocial development of children with a CLA/P.

Despite the lack of sound scientific research, the working group concludes, based on its own experience from clinical practice and feedback from patients during the focus group meeting, that there is a need for psychosocial guidance for parents both for themselves and for their child. The working group therefore believes that the possibility of psychosocial counseling should be part of the standard good care for children with CLA/P, and that it makes sense to screen parents and children for this.

The working group feels screening moments should take place at birth and at important moments of transition in the life of a child with a CLA/P: at the age of two to three years (before school starts), 5 years (before reading start), 10 to 11 years (before transition to high school), 17 years (before transition to tertiary education). At this contact, the screening should focus on child factors (well-being, possible learning and acceptance problems) and family/parent factors (acceptance problems, grief and parenting style). The working group advises that the same validated instrument is used for this screening. Based on the results of the screening, further diagnosis or treatment should be offered to parents and children. In order to offer such screening, a school team must have a post-graduate professional (health care psychologist or general educational expert and social worker, for the less complex issues).

Substantiation

Background

Parents who have a child with a congenital anomaly such as a CLA/P have several reasons to worry about their child's future. Experience has shown that this concern of parents usually starts at the time of diagnosis (prenatal or non-prenatal), and is then present at various times during the development of the child. In clinical practice, it appears that there may be acceptance problems, grieving and concerns about issues such as the social acceptance of the child in the future. The course of guidance to parents (and child) with regard to psychosocial well-being and education is complex and spans over various periods during the development of the child from baby to (young) adult. Although much of the primary treatment is medical/surgical in nature, the ultimate goal of the total treatment of a CLA/P team is the psychosocial well-being of the child with a CLA/P and his or her family. It is therefore desirable to identify whether and when psychosocial support would be beneficial to parents and children and, if so, at what points in the child's development this can best take place.

Conclusions

No assessment	Currently there is insufficient evidence to support any specific psychosocial intervention for individuals with cleft lip and/or palate and their parents. *Norman, 2014*

No assessment	The age of an individual with cleft lip and palate does not appear to influence the occurrence or severity of psychosocial problems. *Hunt, 2005*

Summary of literature

Description of studies

Psychosocial interventions

One study, a systematic review, was included in this literature summary. Norman, 2014 aimed to assess the effectiveness of different psychological interventions for children and adults with cleft lip and/or palate and their parents. Six databases (including Medline and Embase) were searched until June 2013. Studies were included if at least 90% of participants had cleft lip/palate (or parents of children with cleft lip/palate), unless results were reported separately for patients with cleft lip and/or palate or raw data were available upon request from authors. A total of 7 studies were included in this review.

Psychosocial development

For this literature summary the conclusions of systematic review by Hunt, 2005_1 was considered as a foundation. The conclusions from the review were supplemented by the 24 studies published after the systematic literature search of this review was performed (December 2003). No GRADE-assessment was performed of these studies and no literature conclusions were formulated, since the study designs was not suitable for this. However, the studies are described narratively in the paragraphs below.

Hunt, 2005 is a systematic review examining the psychosocial impact of cleft lip and palate among children

and adults. The following specific research questions were assessed: 1) are children and adults with cleft lip and palate at increased risk of impaired psychosocial functioning? 2) What, if any, type of psychosocial impairement do children and adults with cleft lip and palate develop? 3) Is there a relationship between cleft type and the prevalence and severity of psychosocial impairement? 4) Are children with cleft lip and palate more vulnerable to psychosocial problems at particular stages of development? In this review a systematic seach was performed up to December 2003 and found 64 papers that met the inclusion criteria, that were prospective, retrospective or cross-sectional in nature. Only 30 of the included studies had a control group.

Baker, 2008 is a cross-sectional study that examined the role of parent's coping strategies and social support in the family impact of cleft lip and palate and levels of adjustment. A total of 103 parents of children and young adults with cleft lip and palate (age 0 – 18 years) participated in this study, by filling out a Coping Response Inventory, the interpersonal Support Evaluation List – Short Form, the Stress-related Growth Scale, the Family Impact Scale and the General Health Questionnaire.

Berger, 2009 is a cross-sectional study exploring the nature of psychosocial adjustment in youg peaople with a cleft and their parents. A total of 145 participants aged 11 – 16 years and their families were included in this study. Participants completed measures of psychological adjustment, coping, social experiences, satisfaction with appearence, cleft-related factors and demographic information.

Brand, 2008 is a cross-sectional assessed psychological functioning and interactional competencies and sleep patterns in children with cleft lip and palate. A total of 32 children with cleft lip and palate and 34 controls aged 6-16 years old were included in this study. For psychosocial assessment the Strength and Difficulties Questionnaire and a questionnaire on interactional competencies was used. For sleep assessment a sleep log was completed for seven consecutive nights.

Collett, 2012 is a cross-sectional study that aimed to determine whether psychosocial functioning in children with orofacial clefts and their parents differs from unaffected controls. A total of 93 participants with orofacial clefts and 124 controls aged 5-9 years were included in this study. Psychosocial functioning was measured by the Child Behaviour Checklist, the PedsQL 4.0, the Social Competence Scale and the Parenting Stress Inventory.

Demir, 2011 is a cross-sectional study aiming to determine whether children with non-syndromic cleft lip and palate are more likely to be diagnosed with psychiatric disorders and whether cleft-related factors are related to psychopathology. A total of 20 children aged 6-16 years with cleft lip and palate were included in this study together with 40 controls without cleft lip and palate. Children were assessed by psychiatric interviews and by the Child Depression Inventory, State-trait Anxiety Invetory for Children, Piers-Harris Children Self- Concept Scale, Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime version, Ankara Articulation Test, Weschsler Intelligence Scale for Children, Beck Anxiety Inventory and Beck Depression Inventory.

Feragen, 2009 is a cross-sectional study that assessed self-reported social experience in children with a cleft lip and/or palate. A total of 268 10-year old children were included in this study, also their parents were requested to participate. The Child Experience Questionnaire, Personal Inventory for Children and

Satisfaction with Appearence Scales were used to study cognitive, emotional and psychosocial functioning.

Feragen, 2010_1 is a cross-sectional study that investigated associations between percieved peer harassment and satisfaction with appearence in children with a cleft lip and/or palate. A total of 661 children with a cleft (non-visible in 227 patients) aged 10-16 years were included in this study. Peer harassment was measured by the Child Experience Questionnaire. Satisfaction with appearence was measured with the Satisfaction with Appearence Scales.

Feragen, 2010_2 is a cross-sectional study that investigates the role of friendships and social acceptance in adolescents with a cleft. A total of 196 adolescents with a visible cleft, 93 with a non-visible cleft and 1832 controls with no cleft were included in this study. The adolescents aged 16 years filled out the Hopkins Symptom Checklist for depressive symptoms and the Self-Perception Profile for Adolescents.

Feragen, 2014 is a cross-sectional study that explores psychological functioning in adolescents with a cleft aged 16 years. A total of 857 adolescents with a cleft (non-visible in 284 participants) and 1832 healthy controls were included in this study. Cognitive, emotional, behavioral, appearence-related and psychosocial adjustment was assessed by the Hopkins Symptom Checklist, the Harter Self-Perception Scale for adolescents, the Child Experience Questionnaire and Satisfaction with Appearence Scale.

Hentges, 2011 reports a follow-up of the population of Murray, 2007, when the children are aged 7 yeras. Again, cognitive development of children with delayed lip closure (n=49), early lip closure (n=44) and healthy controls (n=77) were assessed in terms of Intelligent Quotient, language and school development.

Corner, 2009 is a cross-sectional study that examined the social-emotional health of children with a cleft performed in the Netherlands. In total 80 children with a cleft, aged 9-12 years were included in this study. The participants, as well as their parents and teachers filled in questionnaires about their social-emotional health: The “Strengt Hand Difficulties Questionnaire”, the “Child Behavior checklist” (parents) and the “Teacher’s Report form” (teachers).

Hunt, 2006 is a cross sectional study that aimed to determine the psychosocial effects of cleft lip and/or palate among children and young adults, and compare those effects to a control group without cleft lip and/or palate. A total of 160 children/young adults aged 8-21 years were included in this study, together with 113 controls. Psychological functioning was assessed using validated psychological questionnaires.
Happiness with facial appearence was rated using the visual analogue scale. Social functioning, including experience with teasing/bullying was assessed using a semi-structured interview.

Hunt, 2007 is a cross-sectional study that aimed 1) to determine the opinion of parents regarding the psychosocial functioning of their child with cleft lip and palate, 2) to identify predictors of psychosocial functioning, 3) to determine the level of agreement between children with cleft lip and palate and their parents. A total of 129 parents of children with cleft lip and palate and 96 parents of healthy controls were included in this study. Children were aged 8-18 (mean 12) years. Sections completed the Child Behavioural checklist, were interviewed and gave their opinion of the child's self-esteem, anxiety, happiness and problems caused by facial appearence using visual analogue scales.

Hutchinson, 2011 is a systematic review and meta-analysis that examined the cross-cultural psychosocial impact of cleft lip and/or palate in non-Anglo populations. A total of 4 studies containing 2276 adolescents and adults with cleft lip and palate were included in this review. The studies were performed in China, Hong Kong, Taiwan and Norway. Effect sizes were estimated using Cohen's d and confidence intervals.

Kramer, 2009 is a cross-sectional study that studied the quality of life and social functioning in schoolchildren with a cleft and their families. A total of 170 children with cleft lip and palate and their families were included in this study. Both child an family were requested to fill in the Impact on Family Scale Questionnaire. The results were compared with age-matched average scores of unaffected children from a control group of 132 families.

Murray, 2007 is an observational study in which the effect of early versus late cleft lip repair are studied on infant development and mother-infant interactions. A total of 94 infants with cleft lip, and 96 control infants were examined. Early lip closure (<1 month) was performed in 48 infants and late lip closure (3-4 months) in 55 infants. Cognitive development, behavioral problems and attachment were assessed at 2, 6 and 12 months.

Murray, 2010 is an observational study that studies the effect of cleft lip on socio-emotional functioning in school-aged children. A total of 93 children with cleft lip (white hand without cleft palate) and 77 controls were included in this study at the age of 18 months, and followed for 7 years. Socio-emotional functioning of children was assessed using teacher and maternal reports, observations of social interactions, and child social representations.

Petrackova, 2015 is an observational study that compares the effects of early versus late exposure to anesthesia on intelligence quotient and psychosocial development in children who were operated for cleft lip. In 15 patient early lip closure, in the first 8 days of life, was performed. In 17 patients late repair, at 3-10 months, was performed. Intelligence quotient and psychosocial development were compared at the age of 3- 7 years.

Roberts, 2012 is a systematic review that examined the cognitive functioning of children and adults with cleft lip and palate or cleft lip or cleft palate only. A total of 29 papers was included in this review, containing data from 1 546 persons with a cleft and 279 805 controls. The included studies showed large heterogenity (age of study population, length of follow-up, measurement of outcome variables). Cohen's d effect sizes were calculated to compare the difference between the cognitive performance of the cleft and control groupsfor the 10 broad cognitive domains. Effect sizes were weighed by inverse variances (corrrected for sample size per study). Due to the large heterogeniety of the included studies, the results of these weighed effect sizes should be interpreted with caution.

Silfer, 2003 is a cross-sectional study in which the social interaction patterns of children with and without clefts were studied. A total of 34 children with oral clefts aged 8-15 years were matched to 34 non-cleft controls (match for sex, age and socioeconomic status). Participatents were videotaped while interacting with a peer confederate. The cleft- and control groups were compared on social behavior.

Speltz, 2000 is a prospective longitudinal study that examines cognitive and psychomotor development in patients with a cleft. A total of 29 patients with cleft lip and palate, 28 with cleft palate only, and 69 healthy controls were included in this study. Infants were administered the Bayley Scales of Infant Development at the age of 3, 12 and 24 months.

Swanenburg de Veye, 2002 is a cross-sectional study which studies the association between associated congenital malformations and the mental and psychomotor development of children with clefts. A total of 148 children with cleft lip (n=56), cleft palate (n=32) or both (n=62) were included. The children's level of development was determined by means of the Dutch version of the Bayley Scales of Infant Development.

Wehby, 2012 is a longitudinal database study (it is not mentioned whether the data collection was prospective or retrospective) that examines behavioral health in children aged 2-12 with oral clefts. A population-based sample of 104 children with oral clefts in the United States of America is used for this purpose. BeHAviour was evaluated using the Child Behavior Checklist or the Pediatric Behaviour Scale 30, depending on age comapred with normative samples.

Wehby, 2014 is a longitudinal database study (it is not mentioned whether the data collection was prospective or retrospective) that compares the academic achievement of children with oral clefts to their classmates in a population-based study in the United States of America. The sample included 588 children with clefts (3744 child-grade observations) and 1874 classmates without clefts (13159 child-grade observations). Differences were assessed at different ages/levels of education (elementary, middle and high school). Academic achievement was essesed by using standardized tests of academic progress developed by the Iowa testing programs.

Results

Psychosocial interventions

Norman, 2014 concludes that out of the 7 included studies only 2 were randomized controlled trials (RCTs) and included for full data analysis (one of which failed to meet the full inclusion criteria). Both of these RCTs were performed in adults (some with clefts), and therefore, not relevant to answering our research question. The five remaining studies were observational and included only in a narrative synthesis, because data were available for people or parents of those with cleft lip and/or palate only. Two studies (Maddern, 2006; n=29 and Kapp-Simon, 2005, n=20) were performed in children (some with clefts) and one in parents of children with cleft palate (Pelchat, 2004, n=76).

Maddern, 2006 described the effect of cognitive behavioral training (CBT) in children with any form of disfigurement aged 5-16 years. A total of 4 sessions was administered by a clinical psychologist or assistant psychologist (duration of sessions not stated). Patients were followed for 6 months after the intervention. At 6 months follow-up children reported a reduction in the frequency of teasing and in the degree of distress it caused both in the classroom and in the playground. Parents reported reductions in their children's somatizing behavior and levels of anxiety.

Kapp-Simon, 2005 described the effect of social skills training (SST) in children with craniofacial conditions

aged 12-14 years. A total of 12 sessions lasting 90 minutes were administered. Children on the waiting list for the SST served as controls. Both target and peer-controlled total communication improved across time with adolescents receiving social skills intervention showing significantly more improvement than those adolescents not receiving direct social skills interventions. Adolescents receiving treatment participated in significantly more target initiated conversations lasting at least three interchanges and showed a trend TOwARDS a greater frequency of target initiations and positive responses to peer initiations. Peers were more likely to respond to treatment subject initiations after intervention. Fewer treatment subjects used nondirected communication, whereas control subjects continued to use nondirected communication at a slightly increased frequency.

Pelchat, 2004 describes a family intervention program (a form of CBT) in parents of newborn children with cleft lip and/or palate and Down syndrome. The intervention consisted out of 6-8 sessions administered by a nurse (duration of session not stated). Parents reported to be significantly satisfied about the intervention program. Parents of children with cleft lip and/or palate were significantly more satisfied than the children of parents with Down's syndrome.

Pooling and meta-analysis of data was not possible due to heterogeneity of the included studies. This review found no evidence to support any specific intervention.

Psychosocial development

Hunt, 2005 summarizes that the majority of adults and children with cleft lip and palate do not appear to experience major psychosocial problems. Berger, 2009; Collett, 2012; Corner, 2009 and Feragen, 2014 concur with these findings. It has to be noted, though, that literature has tended to report the psychosocial functioning of cleft lip and palate children in a general way. This has often disguised specific problems that these children have in relation to adjustment, behavioral problems, self-concept, self-esteem, self-confidence, body image, satisfaction with facial appearence, satisfaction with speech, social life, anxiety, depression and learning problems. Children with cleft lip and palate has been described as more external in locus of control and significantly more field dependent than non-cleft controls. Children with cleft lip and palate also tend to have higher levels of hostility, negative self-worth, a negative outlook and greater dependence compared with the general population. Furthermore, children with cleft lip and palate tend to see their parents as having more negative feelings and worrying more, and adolescents express a lower degree of percieved parental acceptance than controls. Feragen, 2009 reports that psychosocial resilience is associated with adequate emotional functioning, high satisfaction with appearence and a lower frequency of reported teasing.

Self concept appears to be good among children with cleft lip and palate, in some cases even better than in the control group. This concurs with the findings of Kramer, 2009, who reports that children with cleft lip and palate have a better quality of life than the control group. But when present, limitations in quality of life in children with cleft lip and palate mostly affected the social role. However, when specific components of self- concept are examined, some problems emerge. Children with cleft lip and palate may have lower personal and social self-concept scores compared to non-cleft controls.

Self esteem is considered to be generally good among children with cleft lip and palate, although it has been

linked to the child's opinion about facial appearence. Children who are more accepting of their cleft tend to have higher self-esteem, and the more physically attractive a person rates themselves, the higher that person's self-esteem tends to be. Children, adolescents and adults have reported that their self-confidence has been affected by having a cleft lip and palate. Hunt, 2007 reports that self-esteem is lower in children with clefts compared to healthy controls. Regarding timing of cleft lip surgery, Petrackova, 2015 reports that children with early cleft-lip surgery (<8 days) have a better selft esteem that those with late (3-10 months) lip surgery.

Regarding body-image, although most children seem relativeley satisfied, some features (nose and teeth) are considered less satisfactory and may result in problems with body image. There is conflicting evidence about satisfaction with facial appearence, 3 studies report that cleft lip and palate patients are generally pleased with their facial appearence, while 5 studies report that many cleft lip and palate patients express dissatisfaction. Silfer, 2003 also reports that children with clefts and their parents report greater dissatisfaction with facial appearence. A visible scar appears to be of most concern. Likewise, Feragen, 2014 reports that cleft visibility was a risk factor for dissatisfaction with appearence, while Feragen, 2010_1 states that cleft visibility was not associated with appearence dissatisfaction, although this relation is strongly mediated by experiences of peer harassment. Feragen, 2010_2 adds that subjective dissatisfaction with facial appearenc is related to depressive symptoms. Hunt, 2006 and Hunt, 2007 report that happiness with appearence is lower in children with clefts compared to healthy controls, and that this happiness is related to how visible the scar is and whether the child has been teased. Satisfaction with facial appearence has been linked to the incidence
Of behavioral problems, this finding is also reported in Wehby, 2012.

Regarding behavioral problems, there are contrasting reports in children with cleft lip and palate. On one hand, 2 studies reported that children with cleft lip and palate have higher than average levels of internalizing beHAviour (that is a risk factor for developing anxiety problems). On the other hand, 2 studies reported that children with cleft lip and palate are less aggressive than controls and do not exhibit any signs of delinquency.

Patients with cleft lip and palate appear to be more socially affected as a result of having a cleft (as reported by professionals who care for cleft lip and palate patients and self-reports by adults with cleft lip and palate). Several studies performed in the 1970’s have shown that young people with cleft lip and palate are more likely to drop out of school and less likely to belong to a club or society. Also, a larger proportion of adolescents with cleft lip and palate indicate no aspiration for further education, when compared to controls (also study from 1974).

Wehby, 2012 reports that most children with oral clefts had similar behavioral health outcomes as unaffected children, except for increased risk of inattention/hyperactivity ath the age 6-12 years. In contrast, BRAND, 2008 reports that there was no difference in conduct problems or hyperactivity between children with cleft lip and palate and non-cleft controls aged 6 – 16 years. Angle, 2009 also reports that there is less deviant behavior in children with clefts compared to controls with no clefts. Hunt, 2006 and Hunt, 2007 however report that more behavioral problems were reported in children with cleft lip and palate, when compared to healthy controls. Factors associated with behavioral problems were visibility of a scar and having being teased.

No studies regarding anxiety and depression in children with cleft lip and palate were reported, but in adults cleft lip and palate patients had a higher prevalence of anxiety and depression when to controls as assesed by Hunt, 2005. Also, dissatisfaction with facial appearence was found to be a predictor of depression, both among cleft lip and palate patients and controls, this finding is also confirmed in Feragen, 2010_2 and Demir, 2011. Murray, 2010 supplements that children with clefts aged 1.5 – 9 years had raised rates of teacher-reported social problems, and anxious and withdrawn-depressed beHAviour. Corner, 2009 also concludes that there is more depressive behavior as reported by parents in children with clefts aged 9-12 years. Demir, 2011 supplements that social anxiety and major depressive disorder were more prevalent among children with cleft lip and palate than among controls without cleft lip and palate in children aged 6-16 years. However, Feragen 2010_2 reports that boys with a cleft report less depressive symptoms than their peers with no cleft, while overall there was no difference in depressive sypmtoms between 16-year olds with and without a cleft. Both Hunt, 2006 and Hunt, 2007 supplement that more anxiety was reported in children with cleft lip and palate when compared to healthy controls. Teasing was greater among participants who had cleft lip and/or palate and was a predictor of anxiety.

Regarding mother-child attachment, no differences were found between children with cleft lip and palate and controls in the studies described by Hunt, 2005. Likewise, Murray, 2007 reports no significant difference in attachment between cleft lip infants and their mothers versus controls at 18 months. However, some differences (less secure attachment for cleft infants) at 2 months of age are reported.

Regarding development, babies with cleft lip and palate at 5 months of age were found at risk of delayed development. However, at 36 months of age this difference seems to dissipate, except in the area of expressive language. A study from 2000, using both longitudinal and cross-sectional data, found that the difference in mental developmental scores decreased significantly as infants with cleft lip and palate increased in age. Specific learning problems have been described in two studies in children with cleft lip and palate with one study reporting that 1 in every 4 children with a cleft repeated a grade at school. The results of Wehby, 2014 concur with these conclusions: children with oral clefts had lower scores than their classmates across all domains of school levels. Furthermore, children with clefts were approximately one-half grade behind their classmates and had higher rates of academic underachievement. The Dutch study by Hoek, 2009 also reports that 1 in 3 children with a cleft had a learning problem. Timing of lip closure (and accompanying anesthesia) does not seem to influence the intelligence quotient or psychosocial development in patients with cleft lip, as reported by Petrackova, 2015. However, Murray, 2007 reports that late lip closure (3-4 months of age) is associated with worse scores on the Bayley Scales of Mental Development, when compared to neonatal lip closure. Hentges, 2011 supplements that the same infants as in Murray, 2007, at the age of 7 years, score lower on IQ, language and school achievements, compared to healthy controls, particulary those with late repair. Murray, 2010 and Silfer, 2003 also report that social interaction patterns of children with clefts are less developed than those of children without clefts. Also, in adults and adolescents with cleft lip and palate the level of psychosocial development is lower than in individuals without cleft lip and palate in a non-Anglosaxon population, as shown by the meta-analysis Hutchinson, 2011.

The type of cleft and its severity appears to have little influence on the individual's overall psychosocial functioning. No significant association has been found between cleft type and the incidence of behavioral problems, self-esteem, mental and motor development or psychosocial functioning in general. However, a

few differences between cleft types have been found in relation to self-concept, satisfaction with facial appearence, depression, attachment, learning problems and interpersonal relationships. In accordance with the findings of Hunt, 2005, Roberts 2012 reports that the cleft patients score lower than controls on the following cognitive domains: academic, attention/executive function, sensorimotor function, language and general cognition. However, cleft patients score similar to controls on the cognitive domains: Visuospatian, memory (both delayed recall and immediate recall), motor skills and processing speed. Regarding differences in learning problems in relation to cleft type, Wehby, 2014 mentions that children with cleft lip and palate and cleft palate (but not children with cleft lip only) were more likely to use special education services.
Swanenburg de Veye, 2002 reports that children with an isolated cleft palate showed the highes percentage of minor malformations that are minor, yet possibly worry some, while children with an isolated cleft lip showed the least. The children with associated congenital malformations appeared to be most disadvantaged with respect to their development. On the other hand Speltz, 2000 reports (in a slightly smaller sample) that the mental and psychomotor developmental scores of the cleft lip and palate group and the cleft palate only group were lower than those of the control group, but did not differ from one another.

Hunt, 2005 concludes that overall a few differences between cleft types have been found in relations esteem, satisfaction with facial appearence, depression, attachment, learning problems and interpersonal relationships. With a few exceptions, the age of the individuals with cleft lip and palate does not appear to influence the occurence or severity of psychosocial problems. However, the included studies lack uniformity and consistency required to adequately summarize the psychosocial problems resulting from cleft lip and palate.

Age and psychosocial problems
Hunt, 2005 concludes that overall the age of an individual with cleft lip and palate does not appear to influence the occurrence or severity of psychosocial problems. However, there are a few nuances to this conclusion. Increasing conduct problems have been reported as the child grows older. In relation to speech, parents and children with cleft lip and palate have reported increased satisfaction as the child grows older. While individuals of all ages have reported dissatisfaction with their facial appearence, one study did find that younger children and adolescents (age 10-15 years) were less satisfied with their appearence than subjects aged 20 years. Satisfaction with appearence in females has been found to decrease with age among those with inter-oral defects only.

Baker, 2008 concludes that for parents, having a younger child with cleft lip and palate is associated with a greater impact on the family than having an older child with cleft lip and palate.

Hutchinson, 2011 reports that adolescents are significantly less impacted by psychosocial issues than adults, in non-Anglosaxon populations.

Speltz, 2000 reports that in infants aged 3-24 months there is no difference in changes of psychomotor or mental developmental index accross time, when compared to healthy controls.

Wehby, 2012 finds that there is a significant difference ($p<0.05$) in inattention/ hyperactivity risk between children with oral clefts aged 2-5 years (4.4%) and aged 6-12 years (20.3%).

Wehby, 2014 supplements the conclusion of hunt, 2005 that there were no consistent patterns of changes in educational achievements accross school levels (elementary-, middle- and high school).

Grading the evidence
Regarding the psychosocial development, a GRADE or EBRO assessment of the evidence could not be provided, since the research question was not prognostic, diagnostic or intervention-based by nature. Hence, no evidence tables were provided for the studies included in this part of the literature summary.

Regarding the psychosocial interventions, a GRADE or EBRO assessment of the evidence could not be provided, since there was insufficient evidence to support any psychosocial intervention.

Search and select

In order to answer the initial question, a systematic literature analysis has been carried out based on scientific search questions and related PICOS:

What is the effectiveness of psychosocial guidance from a multidisciplinary team for children with CLA/P and their parents?

P: Patients with CLA/P and the parents of patients with CLA/P
I: Psychosocial counseling
C: -
O: Sufficient knowledge about psychosocial aspects of CLA/P, psychosocial well-being of child and parents, quality of life, psychosocial development.

What psychosocial developmental problems occur in children with CLA/P and when do these problems manifest?

P: Patients with CLA/P and the parents of patients with CLA/P
I: -
C: -
O: Sufficient knowledge about psychosocial development of children with CLA/P, development, intelligence and behavior.

Relevant outcome measurements
The working group considered quality of life of the child, adequate psychosocial development, intelligence, presence of behavioral disorders and psychosocial well-being of child and parents as the outcome measures that are critical to decision-making.

The working group considered knowledge about psychosocial development to be an important measure of outcome for decision-making.

Search and selection

A systematic search was performed in the databases of Medline (through OVID), Embase and the Cochrane Library between 1980 and October 21st, 2014 for PICO 1 and between 2000 and March 9th 2015 . This search was aimed to identify systematic reviews, RCTs and observational studies.

For PICO 1 studies were selected if they investigated the effectiveness of psychological interventions on the psychosocial development of children with cleft lip and/or palate and/or their parents. Children were identified as younger than 18 years of age. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: quality of life (of children with cleft palate and/or their parents), psychological/psychosocial development (of children with cleft palate and/or their parents), intelligence, behavioral disorders and knowledge of psychosocial development. For PICO 1: The initial search identified 213 references of which 12 were assessed on full text.. After assessment of full text 11 studies were excluded and 1 study was included.

For PICO 2 studies were selected if they investigated the psychosocial development of children with cleft lip and/or palate and/or their parents. Children were identified as younger than 18 years of age. Data on effect sizes or primary data had to be available for at least one of the outcomes of interest: quality of life (of children with cleft palate and/or their parents), psychological/psychosocial development (of children with cleft palate and/or their parents), intelligence, behavioral disorders and knowledge of psychosocial development.

For PICO 2: The initial search identified 376 references of which 34 were assessed on full text.. After assessment of full text 9 studies were excluded and 25 studies were included. Regarding the psychosocial development, a GRADE or EBRO assessment of the evidence could not be provided, since the research question was not prognostic, diagnostic or intervention-based by nature. Hence, no evidence tables were provided for the studies included in this part of the literature summary.

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html. https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Swanenburg de Veye hf, Beemer FA, Mellenbergh GJ, Wolters WH, Heineman-de Boer JA. An investigation of the relationship between associated congenital malformations and the mental and psychomotor development of children with clefts. Cleft Palate Craniofac J. 2003;40(3):297-303.OBJECTIVE: This research studied the relationship between associated congenital malformations and the mental and psychomotor development of children with clefts.

Wehby GL, Tyler MC, Lindgren S, Romitti P, Robbins J, Damiano P. Oral clefts and behavioral health of young children. Oral Dis. 2012;18(1):74-84. OBJECTIVES: This study examined the behavioral health of young children with oral clefts, and effects of satisfaction with facial appearance, cleft team care, number of cleft-related surgeries, and socioeconomic status (SES).

Wehby GL, Collet B, Barron S, Romitti PA, Ansley TN, Speltz M. Academic achievement of children and adolescents with oral clefts. Pediatrics. 2014;133(5):785-92. Previous studies of academic achievement of children with oral clefts have mostly relied on small, clinic-based samples prone to ascertainment bias. In the first study in the United States to use a population-based sample with direct assessment, we evaluated the academic achievement of children with oral clefts relative to their classmates.

Organization of care for patients with a CLA/P

In the Netherlands, care for patients with a CLA/P has been provided by multidisciplinary CLA/P teams, following the British and Scandinavian example, since the 1960s. The idea behind the establishment of CLA/P teams was and is that the quality of care increases by working together structurally in a multidisciplinary way according to a fixed treatment protocol and working arrangements. Over the years, the number of CLA/P teams in the Netherlands decreased from 23 (Prahl-Andersen, 1983) to 11 (NVSCA registration January 1, 2016). The teams have been united since 1985 in the Dutch Association for CLA/P and Craniofacial Abnormalities (NVSCA). This association, to which all the CLA/P teams are affiliated, aims to optimize the treatment of patients born with CLA/P or other craniofacial abnormalities in a team context within the Dutch-speaking region. To this end, the NVSCA has developed, among other things, a register of patients with CLA/P and/or craniofacial disorders. The NVSCA register has been validated with respect to CLA/P, with and without additional birth defects (Rozendaal, 2010; 2012a; 2012b) and generates important epidemiological data (Luijsterburg and Vermeij-Keers, 2011; Luijsterburg, 2014). Further information is available online at www.CLA/P.nl or www.CLA/P-cranio.nl.
The purpose of this module is to establish criteria for good clinical practice for CLA/P teams in the Netherlands, including criteria for the multidisciplinary composition of the CLA/P teams, team member qualifications and the responsibility of the CLA/P teams for quality control and documentation of long-term outcomes. These criteria are based, as far as possible, on scientific data taking into account existing standards in the Netherlands and beyond.

National organization of care
In the period 2000-2005, the board of the NVSCA actively sought to further improve the quality and consistency of the CLA/P care in the Netherlands by setting up so-called Special Interest Groups (SIG's). These are groups of caregivers of the same specialty, who are active in the treatment of CLA/P and who come together to learn from each other, discuss each other's treatment and results, formulate quality requirements, etc. This initiative has led to the working groups on logopedics and orthodontics, but has not yet expanded to other fields.

In 2012, the NVSCA issued a second edition of the policy paper for the period 2012-2016 (www.CLA/P.nl/nvsca/leden/welkom). This involves improving the quality of care for patients born with a CLA/P and/or craniofacial abnormalities. The NVSCA aims to achieve this quality improvement by, among other things, introducing a cycle of quality visits for the Dutch CLA/P teams and a quality register.

The NVSCA believes that a minimum number of new unoperated patients/ (un)operated adoptive children with a CLA/P per team per year should also be treated in order to guarantee the quality of a team. In line with the advice of the Health Care Inspectorate on the concentration of this high-complex low-frequency care, the NVSCA recommends that at least 20 new unoperated patients/(un)operated adoptive children with a CLA/P must be treated per year in order to optimize the quality of care. The Working Group agrees with this view and therefore does not make any (different) recommendations in this guideline.

Regional and local organization of care

The Dutch CLA/P teams are expected to implement this Directive at regional/local level. The working group believes that a number of minimum preconditions must be met in order to ensure the quality and consistency of the CLA/P care within a CLA/P team. Although the United States does not have nationally-controlled CLA/P care, the American Cleft Palate-Craniofacial Association (ACPA) has given careful consideration to criteria that should be met by the care provided by CLA/P and craniofacial teams. The working group's recommendations in this module on various aspects of the organization of care are based on the latest edition of the ACPA Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or Other Craniofacial Anomalies (2009), the ACPA Standards for Approval of Cleft Palate and Craniofacial Teams (revised version, June 2015) and, to a lesser extent, the NHS standard contract for cleft lip and/or palate services (NHS, 2013). Information from the above sources has been combined with data from the policy note of the NVSCA (2012) and the Directive on Counseling after Prenatally Established CLA/P (NVPC, 2011) (for the latter two documents see www. CLA/P-cranio.nl).

Multidisciplinary composition and functioning of a CLA/P team

At the invitational conference held for this guideline, several parties indicated that they would like the working group to set out a number of requirements regarding both the composition and the tasks and responsibilities of a CLA/P team. Below, the working group describes – in its opinion – the optimal composition of a CLA/P team. In principle, this team of experts can provide the best possible care as described in the directive. The working group expects the Dutch CLA/P teams to look critically at their own composition and use this proposed team composition as a reference framework. It should be noted that some tasks can be completed within a CLA/P team by different disciplines.

Optimal composition of a CLA/P team

In the working group’s opinion, the professionals described below should be included in a CLA/P team for optimal pre- and post-natal care of (future) parents and children with a CLA/P. Efficiency and cost control do not necessarily require all the members of the CLA/P team to attend a meeting. This depends on the age/time in the patient's treatment course. In order to guarantee continuity of care and to function as a 'sparring partner', it is necessary that at least two specialists, both with recent experience in the treatment of CLA/P patients are available for a number of disciplines per CLA/P team (see below). Recommendations regarding the consultation moments for the clinical geneticist, psychologist or NVO general educational expert and pediatric dentist are included in the appropriate modules.

CLA/P team consisting of:

At least two specialists from each of the following disciplines

- Ear, nose and throat specialist
- Logopedic
- Oral, Maxillofacial surgeon
- Orthodontist

- Plastic surgeon

At least one specialist from each of the following disciplines

- GZ-psychologist or NVO general educational expert (pediatric) dentist
- Social worker or CLA/P nursing consultant

Care professional with focus area is available on consultation basis in the care facility:

- Anesthesiologist with supplement pediatric training
- Audiologist Gynecologist and/or sonographer or ultrasound technician Clinical
- geneticist
- Pediatrician
- (Pediatric) Neurologist
- (Pediatric) Psychiatrist
- (Pediatric) Radiologist
- Maxillofacial prosthetist
- Oral hygienist
- Ophthalmologist Nurse
-

Skills of Team Members

The quality of care provided is of paramount importance for patients, parents and professionals. It is therefore essential that all members of the team are competent in the care of patients with CLA/P. However, this module is not about the "scope" of the activities of the individual (para)medical specialist within the team. The training and experience requirements for (medical) specialists within the CLA/P team are determined by the respective scientific associations and their registration committees. These requirements shall be regularly updated.
Each team of experts should therefore ensure that the team members not only have the necessary and up-to-date qualifications and registrations (BIG, RGS, etc.), but also are members of the NVSCA, actively participate in discipline-related (inter)national SICs. This applies in particular to the first two groups mentioned above: Throat, nose and ear specialist, logopedic, oral, maxillofacial surgeon, orthodontist, plastic surgeon, GZ psychologist or NVO, general educational expert, (pediatric) dentist and social worker or CLA/P consulting nurse.

In addition, team members should have regular and recent experience in the treatment of CLA/P. This last point was specifically mentioned by patients and parents during the focus group meeting for the purposes of this guideline. Patients and parents find the experience of team members – especially the

surgeons – more important than a minimum number of patients treated per year. Experience means acquiring knowledge through fellowships, attending congresses, watching/participating with colleagues in the relevant field in CLA/P centers in the Netherlands or globally.

Responsibilities and functioning of the team

The main task of the multidisciplinary CLA/P team is to provide integrated care to the individual patient, to ensure the quality of treatment and to ensure longitudinal follow-up. In general, any patient seen by the team is expected to receive an effective and multidisciplinary treatment plan with the aim of creating the conditions that will allow the child with CLA/P to ideally grow up to an adult without CLA/P stigma. This means a person with a face where the CLA/P is no longer striking, with good hearing and speech, a functional and aesthetic acceptable identity, and harmonious socio-psychological development combined with efficient use of time and resources, both the patient and his/her parents and the health care facility.

In order to achieve the above objective, the following specific principles must be followed by the CLA/P teams (in any order):

Team functioning

- The team has a coordinator, who facilitates the proper functioning and efficiency of the team and helps patients and families coordinate their care and understand and execute treatment plans.
- The team will hold regular (multidisciplinary) consultations (at least once a month) in the physical presence of the patient (and parents).
- The team has arranged prenatal care and counseling, in line with the 'Counseling after Prenatal Adopted CLA/P' guidelines.
- The team is responsible for developing and maintaining an evidence-based treatment protocol and associated care path for children with CLA/P for the relevant prenatal center until the end of treatment at 18-22 years of age, partly based on the present CLA/P Directive and the “Counselling after Prenatally Established CLA/P” Directive.
- The team systematically maintains contacts with the first-line care (such as family physician and dentist), not only of the individual patient, but also with the first-line care from the adherence area as a whole. The team will invite the first line to team meetings if desired/indicated.
- The team maintains a status of each patient, including history, diagnosis, examinations, treatment plans, operating records and supporting documentation such as medical photographs, x-rays, dental models, voice recordings, audiograms.
- The team shall ensure that other health care providers, health insurers, teaching staff, and the general public are aware of and understand the concerns and needs of patients born with a CLA/P and their families.
- The team has regular contact with the relevant patient and parent association and vice versa.

Communication with and partnership of patients and their environment

- The team emphatically involves the patient/parents as a partner in the treatment process and decision-making regarding treatment.
- The team has a dedicated point of contact or has designated one or more team members to make initial contact with patient and parents and to address other caregivers/referrers.
- The team is responsible for ensuring adequate communication of the content of the evidence-based treatment protocol and associated care path with the patient and his environment.
- The team communicates to the patient, parents and referrers which specialist within the team are responsible for certain (surgical) interventions during the treatment course.
- Based on the evidence-based treatment protocol, the team is responsible for establishing a longitudinal treatment plan for each patient, individualized for growth and development, treatment outcomes, patient and environmental burden, and progress in medical engineering capabilities.
- Deviations from the treatment protocol for the individual patient should be described and explained in the patient record and explained to the patient.
- All treatment decisions are weighed against the expected outcomes/results and related factors such as growth in consultation with the patient and his environment
  the facial, hearing, speech, identity, and psychosocial consequences/impact on patient and environment. The
- team/institution provides access to the electronic patient record and/or otherwise communicates the findings, the treatment plan/advice and other recommendations including current information on main treatment with each patient and his/her family in written or digital form as well as in direct presence with patient face to face.
- The team provides information about the (results of) the ongoing treatment to the patient and environment
  and ensures that this information is understood.
- The team ensures that both parents are well informed, while team members are aware that individual parents may have different concerns.
- The team demonstrates understanding and flexibility in providing care to patients and their families who do not speak Dutch, and who come from a different culture or ethnic background. The coordinator shall, if necessary, ensure adequate interpretation of both spoken and written communications.
- When moving to a different region or country, the team facilitates the patient and family to move to another CLA/P team.
- The team provides coaching/guidance to adolescents and their families on completing the (active) treatment and provides information on services available to adults with a CLA/P.
- A CLA/P team should be able to provide the requested care from before birth to adulthood, in such a way that the complete treatment course can be performed even if the patient is over the age of 18.
- The team communicates with the patient upon completion of the CLA/P treatment (between 18 and 22 years of age), where he or she can in the future go for any late onset problems or consequences of the CLA/P. Each team should clearly indicate whether the team has a central entrance (CLA/P team coordinator) for adult patients. If this is not the case, it should be indicated that adult CLA/P care is carried out by the individual specialist medical

practitioner. The working group prefers to keep the CLA/P teams accessible for the late consequences of CLA/P in adults.
- The team is committed to keeping adults with a CLA/P informed about new developments in diagnosis and treatment. This also implies the desire to maintain an up-to-date directory of (old) patients.

Facilities of the CLA/P team

- The team has an administrative location with a secretary and/or coordinator including clear contact details (telephone number and website), which is accessible 24 hours a day.
- The team has a physical location for team consultation hours and for individual patient/parent consultation and for storing non-digital patient data.
- The team/institution has sufficient diagnostic facilities, including at least the ability to take jaw prints from babies, extra and intra-oral photography, 3D stereophotogrammetry, nasendoscopy, performing nasometry, making audiograms, making audio and video recordings of speech, (three-dimensional) x-ray diagnosis including the possibility of performing pharyngograms, and prenatal (ultrasound) diagnosis.
- The team/institution has adequate surgical facilities and associated perioperative care.
- The team is located in a hospital with a pediatric ward and preferably in a hospital with a pediatric center so that the surgical treatment of children of all ages with CLA/P is possible. The team/institution has at least one
- anesthesiologist (preferably more) complying with the standard for operations of children under 2 years of age as described in the Pediatric Anesthesia Directive (under development).

Quality assurance

- The team participates in the central (anonymized) registration of the NVSCA for unoperated new patients and new (un)operated adopted children born with a CLA/P.
- The team will treat at least 20 new unoperated patients per year in accordance with the advice of the NVSCA and to be assessed over a period of 5 years, see also above under the heading Competencies.
- The team systematically evaluates the quality of patient care delivered by the team with the participation of all team members.
- The team/health care facility will conduct periodic examinations of the satisfaction of patients and parents with the treatment provided by the team.
- The team uses external audits by colleagues to evaluate the quality of the care provided by the team and participates in the cycle of quality inspection of the Dutch CLA/P teams organized by the NVSCA.
- The team organizes and documents a complication discussion on CLA/P treatment, which must be attended by all team members, at least 2x a year.
- The team will produce an annual report, which will be sent to the other Dutch CLA/P teams and to the NVSCA. The annual report shall include at least a list of team members with specialization, the number of new

unoperated and previously treated patients from elsewhere who have enrolled, the number of operations/interventions performed, the team's treatment protocol, a summary of the complication record, the results of patient-related outcome measures and finally the results of scientific research and presentations made by members of the CLA/P team on CLA/P-related topics.

Continuous training

- The team ensures that all members of the CLA/P team are members of the NVSCA.
- The team promotes a proactive attitude of all team members towards continuous CLA/P training and encourages and facilitates participation of team members in such training. The working group considers that the members of a CLA/P team should follow a minimum of 8 (post)training hours per year, which are specifically related to CLA/P care.
- The team is committed to early diagnosis of CLA/P in (newborn) children by ensuring adequate training of involved hospital personnel, midwives, neonatologists, but also of primary care personnel and consultancy offices in the recognition of a child with a (palato) CLA/P.
- The team is committed to providing adequate training and information to hospital staff and the first line on critical aspects of the primary care and treatment of a (newborn) child with a CLA/P, including nutrition.

Quality measurement of CLA/P care: documentation and data registration

There is not (yet) a uniform or validated method to measure the quality of CLA/P care and its outcomes. Already in the year 2000, consensus was reached in Europe in the Eurocleft project on a standard documentation set for CLA/P (Shaw, 2001). A number of teams in the Netherlands mostly use this scheme. Recently, these recommendations were also adopted in the US and Canada following the completion of the Americleft project (ACPA, 2013). It was noted that this scheme will be modified in the future. The working group therefore now adopts a pragmatic approach and recommends that the Eurocleft documentation scheme (see above Shaw, 2001) be maintained for the time being, pending further developments in relation to PROMs.

Recently, the International Consortium for Health Outcome Measurement (ICHOM) has developed new outcome measures for CLA/P.[1] The Dutch translation of one of the patient questionnaires (the Cleft Q - patient) is currently being validated. These kinds of instruments make it theoretically possible to compare the results with other centers around the world.
In view of these developments, it is currently impossible for the working group to come up with a detailed guideline about minimum data registration. In anticipation of a structural quality record, the working group advises each team to document a number of matters in a uniform manner both upon the patient's enrollment in the team and at fixed times during and at the end of treatment (22 years). The data must be retained at the time of registration for a minimum of 22 years and must be available at the time of the final evaluation. For the time being, the working group therefore recommends using the Eurocleft documentation scheme.

The working group considers that it is desirable that in the future, expert teams participate in ICHOM or similar systems for PROMs and that participation in PROMs should be part of the checklist to be carried out by the NVSCA during the future quality inspection.

Recent developments in the centralization of CLA/P care in the United Kingdom

The treatment of a child with CLA/P is complex and takes a long time. Given the high variability in the CLA/P types, i.e. sub phenotypes, treatment is never routine and never standard. In addition, the number of children born with this abnormality in the Netherlands including adoptive children is relatively low (n=350-400 per year on a population of 17 million). 20 years ago, people in the United
Kingdom (UK) came to the understanding, based on the results of the EUROCLEFT study and later on the Clinical Standards Advisory Group (CSAG) study, that decentralized and low frequency care were associated with sub-optimal treatment outcomes (Shaw et al, 1992; Bearn et al, 2001). This has led to a strong concentration of care in England, with the number of centers reduced from 57 to 11 to a population of 64 million (Persson et al, 2015).

15 years after this centralization, the results of CLA/P treatment were re-evaluated in the Cleft Care UK (CCUK) study in a similar design to the previous CSAG study (Persson et al, 2015). The results of the CCUK survey have been published very recently (Ness et al, 2015). In summary, the results show that CLA/P treatment has changed over the last 15 years. There is less variability in the surgical techniques used, hearing aids were used more frequently, and fewer eardrum tubes were placed (Smallridge et al, 2015). In the current centralized care setting in the UK, there is a significant improvement in the jaw relationship (Al-Ghatam et al, 2015), speech (Sell et al, 2015) and also - albeit less convincing - for the aesthetic result (Al-Ghatam et al, 2015), while caries prevalence and hearing loss were unchanged (Smallridge et al, 2015). Fewer parents in the CCUK study than in the previous CSAG study indicated that their child has low self-confidence. However, parents' high satisfaction rate with treatment remains unchanged (Waylen et al, 2015). These results show that centralization of care does indeed seem to contribute to a better quality of CLA/P care in the United Kingdom.

Quality Visit

The working group believes that the system of quality inspection and quality registration envisaged by the NVSCA can help to optimize the quality and consistency of the care provided by the Dutch CLA/P teams, where this module can be a guide. The NVSCA's policy note mentions the use of a 5-year cycle. In the long term, the implementation of this Directive may be incorporated into the visitation methodology as a medical audit.
The working group advises the NVSCA to follow the American system for "approval" of teams - as formulated by ACPA - during a visit (ACPA Standards for Approval of Cleft Palate and Craniofacial Teams, 2015 edition). The ACPA defines 6 components, which are considered essential for the quality of care of the team to patients with a CLA/P regardless of the type of CLA/P or craniofacial disease. These items can be verified during a visit. These items are:

1. Team composition
2. Team management and responsibilities
3. Communication with patient, family and referrers
4. Skills with care of patients from minorities and adoption
5. Securing psychosocial care for patients and parents
6. Assessment and documentation of outcomes/results of the treatment

Reporting

Last reviewed: 09-01-2018 Last authorized: 09-01-2018

For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html. https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html .

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Dentistry in patients with CLA/P

Primary question

What is the role of the dentist with affinity to pediatric dentistry in the school team and the skin doctor in dental care for children with a CLA/P?

Recommendation

For the CLA/P team
Include a (pediatric) dentist in the CLA/P team who has an affinity for pediatric dentistry.

Have the first consultation with the dental practitioner of the CLA/P team after breakthrough of the first baby teeth (six to twelve months).

The CLA/P team must check the teeth of children with CLA/P at the age of 5, among others by using X-ray imaging. This is in addition to the periodic monitoring by the family dentist.

Inform the first-line dentist about the treatment path followed by the CLA/P team and decide who will take care of dental care.

For the family dentist
If a child with a CLA/P comes to your practice for treatment, please contact the CLA/P team and consult with them when you feel it is necessary.

Check the teeth of children with CLA/P at least every 6 months.

Considerations

Children with CLA/P often have bad oral hygiene, more gingivitis (Perdikogiammi, 2009; Parapanisiou, 2009) and more caries (Hewson, 2001; Cheng, 2007; Wells, 2013; Antonarakis, 2013) than children without a CLA/P. The pathogenesis of these oral diseases in children with a CLA/P is the same as in children without a CLA/P. However, it is reported that children with CLA/P are more affected by dental anomalies such as agenesias and hypodontics, impactions, abnormal shape of teeth elements and glaze hypoplasias (Costa, 2012; Cheng, 2007; Burke and Shaw, 1992; Bacher, 1991; Jamalian, 2015; Bartzela, 2013). Furthermore, occlusion and articulation may be impaired. In addition to these congenital abnormalities, the increased risk may also be explained by the fact that children with CLA/P often have different dietary habits and/or that children and their parents/carers experience specific problems in the care of the teeth: fear of brushing in the area around the CLA/P, hard to reach areas due to abnormal tooth shape/orientation, practical problems with swallowing, acceptance problems etc. It is recommended that parents and children are more adequately informed about oral hygiene and dietary habits (Wells, 2013; Antonarakis, 2013). The recently published results of the Cleft Care UK study (CCUK) show an average dmft[1] of 2.3, 48% of children were caries-free and 44.7% had untreated caries. Oral hygiene was generally good and 96% of the children were known to a dentist (Smallridge, 2015). However, the literature is not clear on this point. As many articles describe that they were not able to find differences in oral health between children with and without CLA/P (Wong, 1998; Lucas, 2000; Lages, 2004; Hasslöf, 2007).

It is frequently stated in the literature that dental care is of great importance in children with lip, jaw, and/or palate clefts (Madahar, 2013; Sandler, 2014). However, there is little to no relevant literature on how dental care for children with CLA/P should be organized. However, a lot has been written about the increased risk that children with CLA/P have to develop caries and/or gingivitis (Antonarakis, 2013; Cheng, 2007; Dalhof, 1989; Hewson, 2001; Parapanisiou, 2009; Perdikogiammi, 2009; Sundell, 2015; Wells, 2013). The different eruption order, tooth position and tooth shape thus promote the colonization of optional pathogenic micro-organisms in the oral cavity and make maintaining good oral hygiene a challenge.

The oral health care provider should take responsibility for this and will have to take into account the factors mentioned above when providing information and instruction. The information will have to be offered sufficiently individualized ("tailor-made") to be effective in the prevention of oral diseases (Cheng, 2007).

Another area of concern in dental care for children with CLA/P is the establishment of a good relationship of trust between the oral care provider and the children and their parents/carers. Children with CLA/P receive a lot of medical attention and interventions in the oral area from a very early age. This can lead to an increased risk of developing a medical-related anxiety, including a fear of the dentist or the dental setting. A lot of, relatively calm, exposure may be effective in preventing or reducing this anxiety in children (Waaijen, 2001).

In principle, every family dentist should be able to provide adequate dental care (both preventive and curative) to children with CLA/P. However, in the Netherlands, children are usually only seen by the family dentist at the age of 2. More often later, only around the 4th or 5th year of life. This is, in fact, too late to have a real preventive effect from primary information and information. An early dental consultation is therefore necessary for those at increased risk. However, not all oral care practices, and/or oral care providers, are designed to receive such young children. In addition, the current system of reimbursement leaves little scope to cover costs for these purely preventive/informative consults.

This should preferably be performed as part of the oral care for children with CLA/P within the frameworks of the CLA/P team. This mainly involves the very first consultation, assessing the risk profile, making primary diagnosis and providing primary preventive information and details, and arranging follow-up consultations if necessary. In view of the particular health burden of patients with CLA/P, it is desirable that this preventive care is carried out by a dentist with specific affinity for this part of dentistry.

The working group therefore proposes that preferably a differentiated dentist, a so-called dentist pedodontologist, should be included in the CLA/P team. This is a dentist who's a postinitial master's degree in pediatric dentistry. A dentist without this recognized differentiation but with the necessary affinity for children could also fulfill this task.

The dentist in the CLA/P team can thus perform the primary diagnostics, make a risk assessment and draw up an oral care plan for both the short and longer term. The latter will of course be done in consultation/coordination with the other disciplines of the CLA/P team and in consultation with the family dentist so that treatments can be properly coordinated and treatment choices can be made in mutual consultation. A first consultation with the dental practitioner of the CLA/P team should preferably take place around the eruption of the first baby teeth (six to twelve months). This consultation is mainly informative.

The practical implementation of the oral care plan can be carried out in consultation with the parents/carers and, where

appropriate, the child, at the family dentist's practice or at the practice of the dentist (pedodontologist) of the CLA/P team. If there is no family dentist, the dentist or orthodontist of the CLA/P team may mediate in finding a suitable family dentist. The dentist of the dental team will thus have a kind of 'director role' in the implementation of the individual oral care plan drawn up for the relevant patient. It is preferable that the dental practitioner of the CLA/P team sees the patient at certain fixed times. In addition, the dental practitioner of the CLA/P team will have to make himself available at all times for consultation of patients and family dentists in the event of questions concerning oral health, dental development, specific dental treatments, calamities or otherwise.

For proper dental care of the child with CLA/P, the division of roles between the dentist and orthodontist of the CLA/P team and the home doctor should be clear to all concerned. Therefore, the skin doctor will always be informed about the progress of the treatment in general and of the oral care plan in particular from the nursing team. Conversely, if a child with a CLA/P is treated a skin doctor should in practice contact the CLA/P team and consult with the CLA/P team when deemed necessary.

Early diagnosis and prevention are the cornerstones of dental care in children with CLA/P, as explained in the introduction. Children with CLA/P and their parents/carers will have to receive "tailor-made" advice from the CLA/P team in collaboration with dentist, dental hygienist and possibly prevention assistant. The recall period at the family dentist can be set at six months but will be adjusted individually downwards as indicated. The working group recommends, based on Eurocleft, that imaging be carried out at the age of 5 or 6.

At this point, reference is made to the directive "Oral care for the Youth".

It is recommended that the first-line dentist contact the CLA/P team if a child with a CLA/P is treated at the practice and consult with the CLA/P team when deemed necessary. Children with CLA/P are often at greater of developing caries or periodontal problems.

master's degree in pediatric dentistry. A dentist without this recognized differentiation but with the necessary affinity for children could also fulfill this task.

The dentist in the CLA/P team can thus perform the primary diagnostics, make a risk assessment and draw up an oral care plan for both the short and longer term. The latter will of course be done in consultation/coordination with the other disciplines of the CLA/P team and in consultation with the family dentist so that treatments can be properly coordinated and treatment choices can be made in mutual consultation. A first consultation with the dental practitioner of the CLA/P team should preferably take place around the eruption of the first baby teeth (six to twelve months). This consultation is mainly informative.

The practical implementation of the oral care plan can be carried out in consultation with the parents/carers and, where appropriate, the child, at the family dentist's practice or at the practice of the dentist (pedodontologist) of the CLA/P team. If there is no family dentist, the dentist or orthodontist of the CLA/P team may mediate in finding a suitable family dentist. The dentist of the dental team will thus have a kind of 'director role' in the implementation of the individual oral care plan drawn up for the relevant patient. It is preferable that the dental practitioner of the CLA/P team sees the patient at certain fixed times. In addition, the dental practitioner of the CLA/P team will have to make himself available at all times for consultation of patients and family dentists in the event of questions concerning oral health, dental development, specific dental treatments, calamities or otherwise.

For proper dental care of the child with CLA/P, the division of roles between the dentist and orthodontist of the CLA/P team and the home doctor should be clear to all concerned. Therefore, the skin doctor will always be informed about the progress of the treatment in general and of the oral care plan in particular from the nursing team. Conversely, if a child with a CLA/P is treated a skin doctor should in practice contact the CLA/P team and consult with the CLA/P team when deemed necessary.

Early diagnosis and prevention are the cornerstones of dental care in children with CLA/P, as explained in the introduction. Children with CLA/P and their parents/carers will have to receive "tailor-made" advice from the CLA/P team in collaboration with dentist, dental hygienist and possibly prevention assistant. The recall period at the family dentist can be set at six months but will be adjusted individually downwards as indicated. The working group recommends, based on Eurocleft, that imaging be carried out at the age of 5 or 6.

At this point, reference is made to the directive “Oral care for the Youth”.

It is recommended that the first-line dentist contact the CLA/P team if a child with a CLA/P is treated at the practice and consult with the CLA/P team when deemed necessary. Children with CLA/P are often at greater of developing caries or periodontal problems.

[1] Dmft: Decayed, Missing, Filled, Tooth, milk teeth. The sum of the elements in the milk teeth affected by caries lesions shall be expressed in the dmft index. The number of milk tooth elements ('tooth', t) with a cavity ('decayed', d), with one or more fillings ('filled', f), and milk tooth elements lost by caries ('missing', m) are added.

Substantiation Background

Healthy teeth are important because it affects overall health. Several studies have shown that bacterial infections of the mouth are related to diseases such as diabetes and cardiovascular diseases (Garci, 2000; Li, 2000; Otomo-Corgel, 2012). Caries in children is even associated with lagging growth (ACS, 1992, ACS, 1998; ELISE, 1990; Sheiham, 2006), although this relationship cannot be conclusively confirmed (Van Gemert-Schriks, 2011).

However, health cannot be expressed solely in physical parameters, it is also a sense of well-being. The latter is better described as the quality of life and in this the literature reports unambiguously: the quality of life in children is negatively affected by oral diseases such as caries and gingivitis. Pain, sleepless nights, absenteeism and poor eating habits are mentioned (Low, 1999; Versloot, 2006).

Good oral health is therefore considered important for everyone and prevention of oral diseases remains better than cure.

As described in the directive on oral health for young people, early diagnosis and prevention are seen as the core elements of the current oral health care system. The dentist and dental hygiene obviously play a crucial role in this. It is not so much a question of making this prevention better or more, it is a question of offering it differently. Information and preventive measures should be offered "tailor-made" (Ekstrand, 2005; Evans, 2009; Hausen, 2007). The oral health care provider will first need to ascertain the individual (caries) risk of the patient before choosing the appropriate approach to prevent and/or treat caries (or other oral diseases).

Children with CLA/P may be at increased risk of developing caries and gum problems. However, the pathogenesis of both oral diseases is not different from that of children without CLA/P. Good oral hygiene and a responsible diet are of undeniable importance for children in general and children with CLA/P in particular.

This module will discuss what the frameworks should look like for dental care for children with CLA/P in the Netherlands, both in terms of organization and content.

Conclusions

Not applicable.

Literature summary not applicable.

Search and select

No systematic literature search has been performed for this chapter, because the question about the organization of dental care for children with CLA/P was not answered in a search question. The working group has therefore opted for a consensus method.

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Prenatal care in CLA/P

This module is divided into sub-modules that cover the following topics:

- Information to parents and policies for referral in case of suspicion of prenatal CLA/P
- Confidence of diagnosis in prenatal detection of CLA/P by ultrasound.
- Treatment team requirements for prenatal counseling
- Potential for additional birth defects in prenatal examinations when a CLA/P has been identified and the possibilities of further prenatal genetic testing have been identified.
- Counseling in prenatally established CLA/P in a prenatal diagnostic center
- Medical topics during prenatal counseling in diagnosis of CLA/P
- Pregnancy termination in diagnosis of CLA/P
- Location for delivery in the case of prenatally established CLA/P
- Practical matters concerning the birth of a child with CLA/P, such as nutrition etc.
- Requirements for feedback of post-birth outcome in pre-natal CLA/P may reduce the risk of CLA/P by administering
- additional folic acid around fertilization and in the first weeks of pregnancy

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Information provision and referral policy following prenatal detection of CLA/P

Most children are born healthy. Despite this, many prospective parents wonder whether their child will be healthy. Therefore, pregnant women in the Netherlands have the possibility to have a so-called 20-week ultrasound performed before birth, also known as structural ultrasound research (SEO) called ref NVOG quality standard Prenatal screening for fetal abnormalities 2005; NVOG model protocol SEO 2005. During this ultrasound, the child's growth and development is looked at. Serious physical abnormalities may also be seen.
In the Netherlands, the obstetrical aid provider is responsible for the implementation of the SEO. See NVOG Quality Standard Prenatal Screening: "Structure agreed by all the professions concerned" (see “Organization Note of Prenatal Screening”).
Tests conducted are at regional level by eight regional centers linked to the Academic hospitals. Sonographers, trained according to NVOG quality standards (see NVOG Quality Standard Prenatal Screening) perform the ultrasound, which can be a gynecologist (in training), a primary physician, a midwife or a sonographer.
When abnormalities are found, or in doubt, the pregnant person is referred to a (satellite) center for prenatal diagnosis.

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Provision of information to parents by obstetrical care providers at the time of suspicion of a CLA/P

Primary question

What information should the midwife provide to parents at the time of a suspicion of a CLA/P?

Recommendation

If, during the execution of an SEO, there is a suspicion of a CLA/P or a CLA/P is detected by the sonographer, this will be discussed with the prospective parents during the same consultation.

The conversation with parents is limited to the essentials:

- Your child may have a CLA/P.
- A CLA/P is a congenital anomaly with a cleft in the lip and/or a cleft in the jaw and/or palate.
- Refer to website of the CLA/P Association, Erfo Center and CLA/P Working Group.

Pregnant women with a known increased risk of CLA/P (CLA/P in one of a.s. parents; previous child with CLA/P) have an indication for type I advanced ultrasound examination (GUO) in a satellite center for prenatal diagnosis (NVOG guideline indications for prenatal diagnosis 1999).

Considerations

It is clear that the health care provider, who detects the abnormality on the ultrasound, will have to communicate this knowledge to the pregnant person. Therefore, the prospective parents will have to be informed about the suspicion of a CLA/P.
The working group identifies that this could cause tension. On the one hand, the desire of parents for as many answers as possible to their questions and on the other hand, the fact that the midwife or sonographer cannot be expected to have sufficient knowledge available about any pre-natal condition, including CLA/P. Furthermore, little is known after the initial screening about the severity of the CLA/P and about possible additional (structural or chromosomal) abnormalities. If there is little knowledge about CLA/P, it is wise to inform parents as little as possible about this. Misinformation may cause parents more anxiety or unjustifiably reassure them. It would be best for the sonographer or midwife to stick to the essentials.

Substantiation Conclusions

Level 3	Parents need support and unambiguous information after learning about an anomalous ultrasound result. The correct timing of the information provision is unclear. It is likely that this also applies to parents receive the news of a suspected schisis during an ultrasound. *C: Dahl 2006; Aspinall 2002, Lalor 2007*

Summary of literature

No scientific literature has been found specifically about this subject. The main reason for this is that the Dutch obstetrical organization (1st and 2nd or 3rd line) is very different from other countries.
From the more general literature on prenatal counseling of ultrasound abnormalities, it is known that parents are often unfamiliar with the objective of a structural ultrasound examination (SEO). Research into motives for participation in screening tests showed that the majority of parents sought reassurance. They wanted to hear that the baby is healthy and wanted to see the baby. (Dahl 2006) “I wanted a Polaroid of my baby from the ultrasound for the babybook. I also wanted to hear the heartbeat, see the movements, maybe find out the sex of my future child" (a.s. mother, herself a CLA/P patient) (Aspinall, 2002). The parents are therefore sad in their first reaction to the bad news and some are in shock (see module 'Postnatal phase'). As a result, they are usually unable to absorb all the information properly.
The midwife who discovers an abnormality during the SEO should take into account the lack of information of parents and the state of mind and uncertainty of parents. The Lalor study (2007) showed that 38 women who unexpectedly had an abnormal ultrasound result were particularly concerned if the health care provider who performed the ultrasound did not respond to their questions.

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Conditions for optimal referral management from the obstetrical health care provider to a specialized center for prenatal diagnosis

Primary question

What are the conditions for an optimal referral policy from the obstetrical care provider to a specialized center for prenatal diagnosis?

Recommendation

If there is a suspicion of a CLA/P, refer the patient to a specialized (satellite) center for prenatal diagnosis as soon as possible (within one week).
Taking into account the gestational age - preferably for 22 weeks gestational age - in relation to possible karyotyping.

The referrer is responsible for the reference to a prenatal diagnostic (satellite) center for advanced ultrasound examination and possibly additional invasive prenatal diagnosis.

Reference to a prenatal diagnostic center where a CLA/P team and clinical geneticist participate in counseling is necessary.

Considerations

It can be expected that the sonographer or obstetrician is aware of the referral policy for the prenatal CLA/P observed and that the lines with the (satellite) center for prenatal diagnosis are short and functioning properly. The expertise on various diseases should be present in the center to which the prospective parents are referred.
The members of the working group consider it desirable to arrange referral within a week in order to leave parents with uncertainties for the shortest possible time.
It is the midwife's responsibility to arrange this referral. The referral shall be made in accordance with the arrangements in force at regional level, taking into account, of course, the gestational age. Parents should be able to go home with confidence, that the care chain (care path) is functioning properly and that they do not have to worry about logistics.
A few days of uncertainty for the parents between the SEO and the GUO (advanced sound research) and the follow-up ultrasound is (no matter how annoying this may be) inevitable in the current Dutch structure around the 20 weeks ultrasound.
It is to be expected that many parents will search the Internet for more information about CLA/P during this period. It is important to guide parents in this search; possibly in the form of a leaflet and/or a website.

Substantiation Conclusions

Level 3	There are indications that counseling and therefore referral should take place as soon as possible. *C: Rey-Bellet & Hohlfeld (2004)*

Summary of literature

No scientific literature has been found specifically about this subject. According to NVOG guidelines, if a CLA/P is suspected in SEO, the pregnant person should be referred to a prenatal diagnostic (satellite) center for counseling. An abnormal ultrasound finding is the starting point for a series of closely intertwined and time-bound decisions. Amongst other things, the contingency or breakdown of pregnancy and how parents want to inform the people around them (Sandelowski 2005). The referral must be made in accordance with the arrangements in force at regional level while obviously also taking into account the gestational age.
Insufficient specific information was found about the time period between diagnosis and counseling. In the article by Rey-Bellet & Hohlfeld (2004), the authors believe that the counseling should take place as soon as possible. 27% (8/29) of parents considered that two weeks after diagnosis was too long.

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For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html..

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Consultation and information in the (satellite) center for prenatal diagnosis of CLA/P

Primary question

Ideally, how should the further analysis of the abnormality found, decision-making on whether or not to continue pregnancy and related information be shared with the parents in the prenatal diagnostic center?

Recommendation

The referrer should be informed about the findings of the GUO.

Upon confirmation of the diagnosis, the possibility of additional invasive prenatal diagnosis should be discussed with the future parents and - at least in associated CLA/P, the clinical geneticist should be engaged to help continue the trajectory.

In case of doubt about the continuation of pregnancy of both isolated and associated CLA/P, parents must be referred to the prenatal to the regional CLA/P team. This is to properly inform parents before they make a decision. If desired, parents can then be referred to an ‘independent’ psychologist or medical social worker with sufficient experience in guiding decision-making regarding pregnancy termination.

In terms of the choice of the CLA/P team, a team that is integrated in a multidisciplinary out-patient clinic (plastic surgeon, psychologist/medical social worker, gynecologist, clinical geneticist) is preferred.

It must be possible to meet with the CLA/P team within a week. In order to achieve this, it is advisable to organize a multidisciplinary prenatal CLA/P out-patient clinic.

Considerations

In the (satellite) center for prenatal diagnosis, the pregnant person is offered an Advanced Ultrasound (GUO) Type II study (NVOG guideline indications for prenatal diagnosis), in which the entire fetus will be checked again and the biometrics will be performed again. During this test, the probability of a CLA/P will be confirmed. If the suspicion is not confirmed, and no other abnormalities are found, the prospective parents will be reassured and no further diagnosis will be performed. Upon confirmation of the CLA/P, it is assessed whether other fetal structural abnormalities are present and whether there is an isolated or an associated CLA/P. After the diagnosis has been confirmed, additional invasive prenatal diagnostics (amniocentesis) should be discussed and offered to future parents. In isolated CLA/P, the chance of finding chromosomal aberrations is small (see modules 'Additional Genetic Research'). Associated CLA/P have a higher chance of finding chromosomal aberrations than isolated CLA/P (see modules 'Additional Genetic Research'). If the CLA/P is due to underlying chromosomal pathology, reference to a clinical

geneticist is offered for additional counseling. If the couple chooses to abort the pregnancy, this counseling can also take place at a later stage (see modules ‘Counseling in CLA/P in a center for prenatal diagnosis’).
In the case of an associated CLA/P and normal findings in chromosomal studies, the clinical geneticist should also be involved in counseling. This is due to the high probability of underlying genetic syndromes (see modules ‘Counseling in CLA/P in a center for prenatal diagnosis’). In the event that pregnancy is continued when an associated CLA/P has been detected, it is recommended that the delivery takes placed at a center where a clinical geneticist is present. This is also recommended if parents, in an associated CLA/P, opt for a pregnancy termination. Postnatal examination of the neonate or fetus by a clinical geneticist, as well as obduction and possible additional diagnosis (e. g. DNA) would in such a case be necessary for a possible syndromic diagnosis. In this case, as soon as all diagnosis is known, a concluding conversation with a clinical geneticist should take place several months after parturition.
In case of doubt about the continuation of pregnancy, particularly of isolated CLA/P, prenatal reference to the regional CLA/P team should be made. This is to inform parents about the treatment options to form the most complete picture of this condition before deciding whether or not to continue with the pregnancy. If desired, parents can then be referred to an ‘independent’ psychologist or medical social worker with sufficient experience in guiding decision-making regarding pregnancy termination.
Each prenatal (satellite) center for advanced ultrasound must have a direct line with the regional CLA/P team. The way in which this team can be reached quickly should be known. It is important that there are clear local agreements about the referral policy. How quickly the pregnant person and her partner should be referred to a CLA/P team depends mainly on the parents’ wishes. In principle, an appointment should be possible within a week. In order to achieve this, it is advisable to organize a multidisciplinary out-patient clinic (the CLA/P team should include a plastic surgeon, clinical geneticist, psychologist/medical social worker, and gynecologist). However, the likelihood of recurrence of CLA/P can be discussed in detail at a later stage. This is in fact linked to the final diagnosis, which can sometimes only be made post-natally.

Substantiation Background

The (satellite) center for prenatal diagnosis is currently the highest step in the reference structure around abnormalities in SEO in the Netherlands. It can be expected that this center will be as complete as possible in analyzing the congenital anomaly and providing information to parents, and that information will be as objective as possible.

Conclusions

Level 3	It is important that parents are given the opportunity to ask questions and have time to consider different options. *D: Statham (2000)* *C: Sandelowski (2005)*

Level 3	Parents need a trusted advisor who has sufficient expertise about the abnormality. *C: Hunfeld (1999)*

Summary of literature

Little relevant scientific literature has been found, which specifically deals with the subject of CLA/P. It is important that parents are given the opportunity to ask questions and have time to consider the different options (Statham, 2000). In a review of 17 qualitative studies among parents in whom prenatal diagnosis gave an abnormal result, it was found that the majority of parents were looking for information, which was in line with the choice they had made and that they avoided information that might undermine this choice (Sandelowski, 2005). The Hunfeld study (1999) of 24 women who had seen an abnormality on the ultrasound during pregnancy, showed that parents were more satisfied with an aid worker who was able to take the initiative, who they had confidence in and who had sufficient expertise. The same study showed that parents remember information about the location and severity of the condition better than information about the prognosis and the cause. It is striking that there is little or no information in the literature about the role of clinical geneticist in prenatal counseling in CLA/P.

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Reliability of diagnosis in prenatal detection of CLA/P

Primary question

What is the diagnostic value of prenatal ultrasound diagnosis in predicting a CLA/P in the second trimester of pregnancy?

Recommendation

If a CLA/P is suspected based on the ultrasound, it is very likely that a CLA/P is actually present. However, the severity of the CLA/P cannot be predicted 100% reliably. Also, a CLA/P of the palatum cannot be excluded.

Prenatal diagnostic centers and associated satellite centers should preferably have the ability to create a 3D ultrasound.

Considerations

The detection ratio of the 2D ultrasound and the 3D ultrasound for detecting a CLA/P is variable and the scientific research carried out is of moderate quality. However, it is likely that the detection of CLA/P is higher in a high-risk population screened by an experienced sonographer. By a high-risk population, we mean parents who have a higher empirical (repetitive) chance of a child with CLA/P compared to the normal population. The relatively increased risk of a child with a CLA/P in a positive family history has been recently described by two large research groups (Grosen 2009, Sivertsen 2009). These are the only studies that include more than 50,000 people and have a follow-up of at least 30 years. In summary, both studies describe an increased risk of a child with a CLA/P if one of the parents has a CLA/P themselves. The relative risk for first-degree relatives for recurrence of CL was 17-32, for CLP 20-56 and for CP 20-56. The study of Sivertsen et al. concluded that the severity of the CLA/P does not affect the risk of recurrence while the study by Grosen et al. contradicts this.

Substantiation Background

It is important that caregivers involved are aware of the reliability of the current ultrasound techniques for detecting a CLA/P for good parental counseling.
In the Netherlands, since 2007, the structural ultrasound examination (SEO) in the second trimester of pregnancy (between 18-22 weeks) has been part of routine screening. In the Netherlands it is standard practice to use the trans-abdominal ultrasound technique. Currently, more than 90% of pregnant women opt for prenatal ultrasound (Maars et al., 2010).

Conclusions

Level 2	The detection ratio of a 2D ultrasound in the second trimester of pregnancy for the detection of a schisis is likely to be low in a low risk population. The detection rate has risen significantly over the last decade. There were few false positive diagnoses. *B: Chitty et al.et al. (1991), Shirley et al.et al. (1992), Roberts et al.et al. (1992), Stoll et al. (2000), Shaikh et al.et al. (2001), Sohan et al. (2001), Cash et al. (2002), Crane et al. (1994), Levi et al. (1991), Anderson et al. (1995), Hafner et al. (1997), Forrester et al.et al. (1998), Boyd et al. (1998), Grandjean et al.et al. (1999), Stefos et al. (1999), Clementi et al.et al. (2000), Robinson et al.et al. (2001), Wayne et al. (2002), Tonni et al.et al. (2005), Nikkala et al. (2006), Russell et al. (2008), Offerdal et al. (2008).*

Level missing	The detection ratio of prenatal ultrasound in the second trimester of pregnancy for detecting schisis is likely to increase with the experience of the sonographer. *B: Ecker et al. (1999), Crane et al. (1996,) Offerdal et al. (2008)*

Level 2	The detection ratio for detecting CL and CL ± P is likely to be higher than the detection of a palate schisis alone, with no cleft lip (CP), which is virtually zero. This applies both in a low-risk population and in a high-risk population. *B: Chitty et al. (1991), Shirley et al. (1992), Roberts et al. (1992), Stoll et al. (2000), Shaikh et al. (2001), Sohan et al. (2001), Cash et al. (2002), Crane et al. (1994), Levi et al. (1991), Anderson et al. (1995), Hafner et al. (1997), Forrester et al. (1998), Boyd et al. (1998), Grandjean et al. (1999), Stefos et al. (1999), Clementi et al. (2000), Robinson et al. (2001), Wayne et al. (2002), Tonni et al. (2005), Nikkala et al. (2006), Russell et al. (2008), Offerdal et al. (2008), Wang et al. (2007), Chaimt et al. (2002) , Johnson et al. (2000), Hanikiri et al. (2006), Rotten et al. (2006), Chen et al. (2001).*

Level 2	The detection ratio of a 2D ultrasound in the second trimester of pregnancy for detecting an isolated schisis is likely to be lower than the detection ratio for detecting a schisis with associated anomalies. *B: Hanikeri et al. (2006), Sohan et al. (2001), Wayne et al. (2002)*

Level 2	In a high risk population , with a routine 2D ultrasound, the detection ratio of a schisis is high. It seems likely that an additional 3D ultrasound improves the prenatal classification of a schisis. *B: (2000), Hanikiri et al. (2006), Rotten et al. (2006), Chen et al. (2001)*

Summary of literature

In general, the studies are of moderate quality and several potential sources of confounding were identified:

1. A large part of the studies were retrospectively performed, which gives a high risk of potential bias.
2. Many studies assumed a birth cohort in a certain period. However, researchers cannot verify that all these mothers have actually undergone a prenatal ultrasound. These studies pretend to be prospective, but are inherently retrospective. The follow-up in most studies was not complete, so the exact number of erroneous negative and positive diagnosis is unknown. As a result, conclusions could only be drawn on the detection ratio and not on specificity.
3. The inclusion of pregnant women was not pure, which means that referred women may also be included in the study population (spectrum bias).
4. There was a variation in the size of the study population and the mean gestational age at which the prenatal ultrasound was performed.
5. Some studies precluded the case with an isolated palatum CLA/P, which could potentially increase the detection ratio.
6. The expertise of the sonographers performing the prenatal ultrasound varied greatly. The detection ratio of the prenatal ultrasound depended heavily on the ultrasound technology and the experience of those performing the ultrasound (Ecker et al., 1999). It was also important whether a standard evaluation of the fetal face is used in prenatal screening.
7. There was variation in the definition of the outcome. For example, some studies did not distinguish between isolated CLA/P and CLA/P with additional conditions and the difference between the detection of bilateral and unilateral CLA/P.

The consequence of these differences in set up of the study was a large variation in prenatal ultrasound detection ratio for the determination of a CLA/P in the available literature. This did not make it easy to formulate a clear conclusion. The variation in results will be discussed below, a summary can be found in Tables 1 and 2 (evidence tables). The results have also been analyzed in the review of Maarse et al. 2010.

1. What is the diagnostic value of a two-dimensional ultrasound in the second trimester of pregnancy in the detection of CLA/P in a low-risk population?

21 studies were included, published between 1991 and 2008, which investigated the reliability of 2D ultrasound in detecting CLA/P in pregnant women in a low-risk population. Seven studies are retrospective (Shaikh 2001, Cash 2001, Chitty 1991, Roberts 1993, Shirley 1992, Sohan 2001,
Stoll 2000) and fourteen studies prospectively (Boyd 1998, Clementi 2000, Forrester 1998, Grandjean 1999,
Hafner 1997, Levi 1995, Nikkila 2006, Offferdal 2008, Robinson 2001, Russell 2008, Stefos 1999, Tonni 2005, Wayne 2002, Anderson 1995) performed in a cohort study. One clinically randomized trial was identified, which was added in the prospective studies, as only the results of the intervention group were used.

The 2D ultrasound detection ratio for detecting total number of fetuses with a CLA/P ranged from 0% (Roberts 1993) to 70% (Sohan 2001) in the retrospective studies. The 2D ultrasound detection ratio for detecting total number of fetuses with a CLA/P ranged in the prospective studies from 9% (Forrester 1998) to 73% (Robinson 2001), for isolated CLA/P of the lip or combined with

palate CLA/P (CL ± P) from 9% (Nikkila 2006) to 100% (Tonni 2005) and the detection ratio of primary CLA/P of the palatum without cleft lip (CP) from 0% (Forrester 1998, Offerdal 2008, Russell 2008, Anderson 1995) to 7% (Clementi 2000).

Two high-quality prospective cohort studies were identified, investigating the detection ratio in an unselected low-risk population. Russell et al. examined 108,220 births in the period from 1992 to 2002 that had undergone an ultrasound between the 18th and 20th week of gestation (screening of fetal face was a standard component in this study). The detection ratio for the detection of CL ± P was 23% (29/127). CLA/P of the palatum without cleft lip was not diagnosed prenatally (0/100). The prenatal detection ratio increased significantly when comparing periods 1992-1996 and 1996-2002, 14% versus 30%, respectively (p = 0.03). Also in the study of Offerdal et al. the detection ratio increased significantly between periods 1987-1996 and 1996-2004, from 34% to 58%, respectively, (p = 0.03). This study investigated 49,314 births, with the pregnant women having a routine ultrasound in the 19th week of pregnancy (range 10-40). CL ± P was demonstrated prenatally in 34 of 77 cases, resulting in a detection ratio of 45%. 24 cases were detected during routine ultrasound resulting in a detection ratio of 31%.

The increase in the detection ratio can be explained by the introduction of additional scan levels in the mid-90s. In addition, it became more and more standard practice to scan the fetal at the prenatal ultrasound. So there's an increasing learning curve from the sonographers.
The specificity of the studies was generally high, in eleven studies the specificity for detecting the presence of a CLA/P was 100%.

Some studies only included cases of isolated CLA/P. Other studies also analyzed cases of CLA/P with additional anomalies (both chromosomal and non-chromosomal). The detection ratio for detecting an isolated CLA/P was lower than the detection ratio for detecting CLA/P with additional other structural abnormalities. This can be explained by better targeted screening after finding another condition.

2. What is the predictive value of a two and three dimensional ultrasound in the second trimester of pregnancy in the detection of CLA/P in a high-risk population?
Six studies (Chen 2001, Hanikeri 2006, Rotten 2004, Chmait 2002, Johnson 2000, Wang 2007) were found that analyzed the detection ratio for detecting a (type of) CLA/P with a 3D ultrasound. All of these studies had a selection bias. The patients who were false negative in routine screening were not included (negative index), thus describing only the detection ratio and not sensitivity and specificity. In addition, the selection bias resulted in an artificially increased detection ratio. However, this ratio was relevant for pregnant women who were referred. Therefore, these studies were included in the study.
Six studies were included, three of which were retrospectively performed (Chen 2001, Hanikeri 2006, Rotten 2004) and three studies were prospectively performed (Chmait 2002, Johnson 2000, Wang 2007). All studies had small study populations (N = 21-218). The gestational week during which ultrasound was performed ranged from week 15 through week 39.
Hanikiri et al. found a detection ratio of 41% (39/96) for unilateral CLA/P and 44% (8/18) for bilateral

CLA/P. All 3D studies showed a 100% detection for CL, with the exception of Rotten et al. study (87%). Three studies reported unilateral CL ± P detection at ratios of 88% (37/42) (Rots 2004) and 90% (18/20) (Rots 2004) for bilateral CLA/P and 3D 90% (37/41) (Chmait 2002) and 86% (19/22) (Johnson 2000). Two studies investigated the detection of CP with a variation of 0% (0/95) (Hanikeri 2006) to 89% (19/22) (Wang 2007) with 3D ultrasound.
In the study of Chen et al. and the study of Wang et al. the improvement for detecting the type of CLA/P with a 3D ultrasound compared to a 2D ultrasound was significant (P= <0.05).

In the above studies, CLA/P was shown at a mean gestational age of 24.4 weeks. In the Netherlands, pregnant women usually get their second trimester ultrasound earlier in pregnancy. This makes it more difficult to detect a CLA/P.

Search and select

Identification of the studies
Literature was systematically searched for in Medline and EMBASE. The following terms were used in the search strategy: 'cleft' AND 'ultrasound' OR 'screening' OR 'sonogram' AND 'prenatal' OR 'antenatal' OR 'fetus'. This resulted in 192 and 296 citations, respectively. After deduplication and checking the titles for relevance, 66 studies remained (see flowchart under search report).

Categories
Two categories of studies were distinguished: studies that included an unselected group of pregnant women with a low a priori probability of a child with a CLA/P (low risk) and studies that included only pregnant women, referred due to a suspected child with a CLA/P (high risk). It can be expected that the latter group has a higher risk of a CLA/P (higher a-priori probability). Not only the pregnant women referred to are in this latter group, also the women with a positive family history. If a first degree relative has a CLA/P, the likelihood of recurrence is higher compared to the normal population. Both research groups can be found in the Dutch situation; first line versus ultrasounds in centers for prenatal diagnosis (NVOG quality standard Advanced ultrasound research).

In fact, this creates two basic questions.

1. What is the diagnostic value of a two-dimensional ultrasound in the second trimester of pregnancy in the detection of CLA/P in a low-risk population?
2. What is the predictive value of a two and three-dimensional ultrasound in the second trimester of pregnancy in the detection of CLA/P in a high-risk population?

Inclusion criteria
The study population consisted of pregnant women undergoing ultrasounds (index test) in the second trimester of pregnancy. The study focused specifically on the detection of CLA/P. The results of SEO were then compared with neonatal findings in physical examinations or an autopsy report (reference test). Since CLA/P is a low incidence abnormality, the working group has decided to include studies with a study population = >1000. Only

studies published after 1990 were included, as the difference in ultrasound technology in the previous period is considered to be too great in comparison to today. Finally, the study population in these last studies was to be larger than ten pregnant women.

Quality control

The initial exclusion and assessment were carried out independently by two reviewers (W.M. and T.B.). The quality of the studies was checked by evaluating the study design; among other things, the availability of index and reference tests, the means of inclusion and follow-up failures, as described by Bossuyt et al (2003).

The search strategy in the literature yielded 461 citations, of which 34 articles remained after screening the titles and abstract based on relevance and inclusion criteria. The full text of these were read and critically assessed for their quality.

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Requirements for the CLA/P team for prenatal counseling in CLA/P

Primary question

What requirements (structure, composition, accessibility, experience volume) can be imposed on the CLA/P team in view of prenatal counseling to parents?

Recommendation

It is recommended that the prenatal counseling is given by team members who are not only familiar with the condition and treatment, but also trained in the process that parents should go through when learning the diagnosis. Two team members must preferably provide the counseling, where on the one hand there should be direct knowledge of the (surgical) treatment, and on the other hand, sufficient knowledge of the psychosocial aspects of having a child with a CLA/P should also be available.

CLA/P teams must be easily accessible for the provision of additional information or counseling during the antenatal trajectory. This implies that tertiary centers should preferably have a permanent team of experts to be referred to, so that those doing the referrals and members of the team involved in counseling know each other and so that agreements have been made and written on referral and access.

The additional information and counseling in the antenatal trajectory should be achieved as soon as possible, but no later than within two weeks, in the case of uncomplicated CLA/P; additional complications of the CLA/P and/or considerations regarding pregnancy termination within a few working days.

The development of a clear structure, such as special consultation hours for prenatal counseling, initiated by the CLA/P team is recommended.

Clinical genetics should always be involved early in the event of CLA/P and additional abnormalities (either through the gynecologist or through the team).

In the context of quality assurance in the prenatal counseling process, the working group recommends reducing the number of CLA/P teams in the Netherlands and linking them to the 8 tertiary centers for prenatal diagnosis.

Considerations

CLA/P teams by nature focus on counseling and treatment of a CLA/P after birth. The advancement in technology and the introduction of structural ultrasound research have led the CLA/P teams in the Netherlands and elsewhere to see an increase in the demand for information in the prenatal phase on CLA/P and additional abnormalities.
It can be expected that CLA/P teams anticipate this, by being easily accessible to both the referrer and the patients referenced in the prenatal trajectory. A survey sent to all the Dutch engineering teams in 2007 revealed that not all teams were currently in the process of this turnaround (Mink van der Molen, lecture NVSCA 2007).

To ensure the referral runs smoothly, it is recommended that every tertiary center in the Netherlands (or a satellite thereof) has a permanent team of experts in the region, who patients will be referred to.
In some teams, the demand for prenatal counseling has become so great that these teams, together with the gynecologists (referrers), have set up specific consultation hours to offer prenatal counseling in a structural way (Mink van der Molen, 2010). This will allow regular members of the team to meet their counseling needs in a timely manner. The reference lines are then also short and known to everyone, so that - if the situation so desires - counseling outside the regular structure can also be available at very short notice (several days), for example in case of considerations relating to abortion of pregnancy. It follows that it is preferable for referrals and team members involved in the counseling to know each other and that agreements have been made and written on referral and access. As such, the CLA/P team then becomes part of a care path, as it should initially have been developed (at the end of 2006) on the advice of the Minister of VWS for, among other things, facial abnormalities and that Exalto et al. (2009) made a proposal for. The Minister of VWS has so far not imposed any binding obligation on the implementation of such a care path.

No information has been found in the literature, which members of the CLA/P team are best suited to perform the prenatal counseling, other than that knowledge of the process parents go through in learning the diagnosis for the birth professionals (the team) can help in caring for these families. In the opinion of the working group, counseling should be carried out by at least two members of the team, on the one hand with a direct knowledge of the (surgical) treatment, and on the other hand, sufficient knowledge about the psychosocial aspects of having a child with a CLA/P must also be available. This is all the more true if there are considerations relating to pregnancy termination. Counseling by two members also reduces the risk of bias in the provision of information. There should always be an opportunity to consult the other members of the team.

No minimum criteria for experience or number of patients (parents) for prenatal counseling by CLA/P teams have been found in the literature. In contrast, the Central Organ Prenatal Screening has established minimum criteria for initial counseling regarding participation in the prenatal screening or not (minimum 50/year). The working group considers that the quality of the prenatal counseling from the CLA/P team and the proper functioning of the associated structure (consultation hours, accessibility, leaflets, website, etc.) is also in the interest of adequate routine and experience and should be evaluated regularly.

In England it has been stated that good multidisciplinary treatment of a child with a CLA/P is best done by a team, which sees at least 50 new CLA/P patients per year. The number of 50 new patients with a CLA/P per year would imply that only 5-6 teams of the current 14 teams would remain in the Netherlands. Partly in the context of the already established and well-functioning national structure of 8 university centers and their satellite centers for prenatal diagnostics, it seems obvious to link these centers for prenatal diagnostics and CLA/P teams. This way, a clear and unambiguous reference structure can be maintained per tertiary center, while

at the same time, the desired routine and experience in the prenatal counseling is guaranteed per team. Based on such a choice and in the knowledge that approximately 70% of children with a lip (jaw and palate) cleft are currently diagnosed, this means 20-25 prenatal conversations per CLA/P team per year. The working group estimates that this will be sufficient, with 20 referrals per year considered as the minimum acceptable lower limit for maintaining sufficient experience in prenatal counseling in CLA/P.

Given the increasing role of the clinical geneticist in the counseling process, as reflected in the Directive, all Dutch CLA/P teams should have a (fixed) clinical geneticist.

Substantiation Background

The Netherlands currently has 14 CLA/P teams. The introduction of SEO from 2007 onwards has caused a significant increase in the number of prenatally established CLA/P. In this context, the role of the team has also changed. Counseling was always done after birth, now a significant part of the counseling is done before birth. This requires a different role of both the referring gynecologist (see module 'Diagnostic reliability') and the team in relation to the counseling process.

Conclusions

Level 4	Hard (scientifically based) criteria for the speed of availability of the counseling schisis team were not found in the literature.

Level 4	Knowledge of and experience of the process parents are going through leads to better care for this group. *D: Nusbaum (2008)*

Summary of literature

CLA/P is such a complex disease with so many different and time-related facets in treatment that a multidisciplinary approach is required to achieve an optimal result (Williams et al 2001, Prahl 2005, Wellens 2006, Kasten et al. 2008). Tindlund et al (1997) summarize the international consensus on a number of elements that should be met by a team of experts, such as:

1. Multidisciplinary approach
2. Centralization
3. Continuity of care provided
4. Long-term treatment planning (from child to young adult)
5. Documentation
6. Evaluation results
7. Outcome studies
8. Scientific research
9. Quality control

10. Prenatal counseling

The advantage of multidisciplinary teams, over individual providers of CLA/P care, was recently made plausible in the United States (Austin et al, 2010).
In the Netherlands, the CLA/P care is also provided by teams. The Netherlands currently has 14 CLA/P teams for a population of 16.6 million and an average of 300-350 new children with CLA/P per year. However, following a thorough reorganization of the number of CLA/P teams in the United Kingdom in 2002, questions were also asked in the Netherlands about the optimal number of CLA/P teams and the minimum number of new patients that a team should treat per year (Prahl 2005; Prahl 2010), without any restrictions or other measures to date.
No hard criteria for the speed of availability of the counseling CLA/P team were found in the literature. Davalbhanka and Hall (2000) have a period of 2 weeks (until the next CLA/P consultation hour). Kuttenberger et al. (2010) in the context of postnatal counseling, stress not only the importance of fast information provision, but also the direct establishment of a good long-term relationship between the family and the team, because treatment usually extends over many years and this is unaffected in the prenatal phase. Knowledge of and experience with the process through which parents go leads to better care for this group (Nusbaum 2008).

Search and select

Identification studies
Medline was searched for articles in English, Dutch and German in the period 1995-2010. The following terms were used in the search strategy: Cleft team counseling. This yielded 22 articles, of which 13 studies were of varying relevance after selection. Further restriction with the prenatal search term limited the number of relevant items to 6.

Randomized prospective comparative studies were not found. Most studies are retrospective (often through questionnaires) or describe a (personal) experience of the authors with the team approach and /or counseling.

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Additional anomalies in prenatal counseling in CLA/P

Earlier in this directive it is described that the cleft lip/jaw detection rate with or without cleft palatum (CL ± P) with 2D and 3D ultrasounds is reasonably high, as opposed to the cleft palatum detection without cleft lip/jaw (CP) (see module 'Information provision'). The shell category and severity are important as they are related to the prognosis of treatment and quality of life after birth.
Even more important for the prognosis is the presence of other structural abnormalities as this may indicate a possible chromosomal abnormality or detectable syndromal disease.
It is expected that an isolated CLA/P will be observed prenatal in a larger number of patients with SEO, and further development in the ultrasound examination. In the absence of additional anomalies, growth retardation and prenatal obstetric complications, these were not previously detected. The group of patients with prenatally detected CLA/P in SEO is likely to be a different population than that studied in the studies conducted to date for additional anomalies and chromosome abnormalities in prenatally determined CLA/P. The studies were mainly carried out in tertiary centers for prenatal diagnosis.
It is therefore important to be informed about the percentage of additional anomalies and chromosomal abnormalities in prenatal as well as in postnatally established CLA/P. A targeted literature search has been performed for both prenatal and postnatal CLA/P population.
Of course, it is very important to be informed about the number of additional anomalies and chromosome aberrations within the Dutch CLA/P population. Thanks to the NVSCA, data from the NVSCA registration has been made available for this purpose. In this registration, the type of CLA/P, additional anomalies present, chromosome aberrations and syndromic diagnosis are recorded in a standardized manner for the CLA/P patients.

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Additional genetic studies in the prenatal counseling of CLA/P

Primary question

When is the pregnant woman eligible for additional genetic testing if a CLA/P has been diagnosed in the child prenatally?

Recommendation

It should be concluded that there are currently no suitable studies directly from which the recommendation on additional genetic testing in prenatal CLA/P can be derived. The recommendation is based on the available literature in combination with the considerations described and is at expert opinion level. In view of this, the working group recommends that:

In prenatal CLA/P, a good family history should be obtained, aimed at identifying possible teratogenic causes of CLA/P, and a chromosome aberration or syndromal disorder within the family, of which CLA/P may be part.

In prenatal established *CL without* **associated anomalies**, invasive diagnosis is not indicated, but should be provided.

In prenatal-diagnosed *CLP with no* **associated anomalies**, caution with regard to invasive diagnosis is advised. The possibility of prenatal cytogenetic or molecular genetic diagnosis should be discussed.

In prenatal-determined *CP*, prenatal cytogenetic or molecular genetic diagnosis where a deletion of 22q11 can be detected is indicated. Consultation of a clinical geneticist is required.

Prenatal *median cleft* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Research should be sought with a short results period.

In prenatal *median cleft*, the GEO should focus on the presence of hypertelorism, hypotelorism, microcephalhaly, holoprosencephalie, frontal/basal encephalocele and corpus callosum agenesis.

Prenatally diagnosed *CLA/P with associated anomalies* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Multidisciplinary consultations (including gynecology, clinical genetics, clinical cytogenetics, pediatrician and plastic surgeon) should be conducted.
Research should be sought with a short results period.

If a mandibula hypoplasia is detected, a clinical geneticist should be consulted.

Scientific studies should be conducted in the Dutch population to investigate the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P, with good and long-term follow-up of these patients. For this, good national registration is essential, with both prenatal and postnatal data recorded in a database.

This will also include consideration of whether (targeted) array CGH or MLPA are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

The results of this study are of great importance in order to adjust the recommendations for additional diagnosis in prenatal-established CLA/P to appropriate and suitable dates.

Considerations

1. Literature

The literature search shows that there is no good study of a CLA/P population in which prenatal extensive ultrasound and additional genetic research has been carried out, using recent research techniques, and with a good and long-term post-natal follow-up.
It is not always clear to what extent the family data are involved in the diagnosis in the studies discussed.
There is a large spread in percentage of identified associated and chromosome aberrations. This distribution is based on differences in research design, study population, performing additional studies and reporting the data.

2. Diagnostic description

In the literature, Nyberg et al.'s type 1/5 ultrasound classification is often used (1995). However, in this format, the median cleft with hypertelorism is missing. Type 5, a lateral facial cleft next to a normal nose, has many variations and, like the median cleft, involves a craniofacial abnormality with hypotelorism and hypertelorism, respectively. A correct classification based on embryological development and genetics is of great importance for further policy (see Figure 1 in module 'Definition').
Median cleft often lacks additional information to properly classify the abnormality. In particular, it is necessary to be informed about the presence of hypotelorism or hypertelorism. Hypotelorism in median cleft indicates a condition in the cyclopen series (this is primarily a brain disorder), hypertelorism in median cleft may indicate craniofacial dysplasia. Therefore, the presence of hypertelorism, hypotelorism, microcephaly, holoprosencephalie, frontal/basal encephalocele and corpus callosum agenesia should be addressed in the GUO when detecting median cleft. A good diagnosis can sometimes only be made postnatally. This requires a reference to a craniofacial team and consultation of a clinical geneticist.
As previously indicated, median cleft with hypotelorism (cyclopes/holoprosencephaly series) and hypertelorism (synonyms: median cleft face syndrome/frontonasal dysplasia/bifid nose with median cleft lip), respectively, are not included in the NVSCA CLA/P registration.
Prenatal studies do include median CLA/P, which results in higher trisomies in these studies, among other things.

3. 3-D ultrasound

3-D ultrasounds were not structurally used in the studies. It is not known with certainty how likely it is that after 3-D ultrasound important additional anomalies will be missed and that additional genetic research will be wrongly abandoned.

4. Syndromic diagnostics

CLA/P can be part of more than 600 syndromes, including chromosome aberrations and microdeletion images (about 6% of syndromic diagnosis). When diagnosing syndromic diagnosis, a good family history can be crucial.
A good family history, if necessary in consultation with a clinical geneticist, should be obtained when detecting a CLA/P. The history focuses on possible teratogenic causes of CLA/P and the determination of a familial chromosome translocation or syndromal conditions associated with CLA/P within the family.
It is also important that newborns with CLA/P are seen by a clinical geneticist for further dysmorphological examination. Based on the physical examination, targeted additional genetic diagnosis may be considered.

5. Genetic research techniques

As mentioned, several new techniques have been introduced in recent years that can also detect chromosomal microdeletion images and confirm syndromal images, including MLPA and array- CGH research.
These new research techniques have not been used in the available studies. It is not known exactly how large the percentage of abnormalities will be when these techniques are applied in prenatal diagnosis. Further scientific research is important for this.
At present, there are regional differences in the choice of genetic research techniques within prenatal diagnosis. The scientific association VKGN, in collaboration with the NVOG, is working on a uniform policy, based on careful technical but also ethical considerations. The advice should provide guidance on prenatal cytogenetic or molecular genetic diagnosis in prenatal CLA/P.

6. Scientific research and follow-up

Scientific research and follow-up on the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P is of great importance in order to adapt the recommendations on additional diagnosis of prenatal CLA/P in the future to appropriate techniques and appropriate data. The occurrence of postnatal-associated abnormalities following a prenatal alleged isolated CLA/P is especially interesting. For this, good national registration is essential, with both **prenatal** and **postnatal** data recorded in a database.

This will also include consideration of whether (targeted) array CGH or MLPA studies are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

Substantiation

Conclusions

Conclusion literature genetic research techniques

Usoegawa et al. (2008) Investigated 187 schisis patients, both syndromal and non-syndromal, with array CGH studies. In 5%, a microdeletion was detected (6 Van der Woude patients; 1 syndromal schisis, 1 22q11 deletion; 2 non-syndromal schisis).

Sivertsen et al. (2007) using MLPA studies, detected a deletion of 22q11 in 1.8% of CP patients.

Summary of literature

Literature review has shown only a small number of appropriate studies published in which structural ultrasounds have been performed on additional anomalies and chromosome aberrations in prenatally established CLA/P. There is only one study (Chmait et al. 2006), with a small study population, which investigated how often a CLA/P is mistakenly considered isolated after an extensive ultrasound examination. A large number of (severe) abnormalities were missed on the prenatal ultrasound, which raises doubts about the technical ability of the sonographers in this study. The quality of the study was considered insufficient and therefore not further reflected in the Directive.

Methodological aspects in relation to the available literature

A: Review according to the literature (earlier review) (Wyszynski et al. 2006):

At least 50 publications have been published on the pre- and postnatal prevalence of additional anomalies in addition to CLA/P. The differences in methodological design lead to a large variation in the results of these studies (Wyszynski et al. 2006). This is due, among other things, to variation in:

1. Definition

Some studies define additional anomalies as ‘all proven syndromes’ and some as ‘all minor and major malformations found in addition to the CLA/P’. In addition, many studies exclude submucous CP (which does not seem correct, because a submucous cleft has been embryologically formed after the fusion process of the palatini process due to a disorder in the differentiation process of bone and muscle tissue, a process similar to a differentiation disorder of the primary palatum resulting in an incomplete/submucous cleft of the lip and/or jaw; see 'definition’ module).

2. Inclusion criteria

There is a difference in inclusion criteria in the postnatal studies. There are studies that only include live-born children. Other studies include both live and stillborn children, children who died in the neonatal period and fetuses whose pregnancy was terminated. There are also studies with a retrospective study design and studies with a prospective study design.

3. The follow-up period after birth

Not all additional anomalies present in the first year of life. Certain phenomenon, such as 22q11.2 deletion syndrome [Velo-Cardio-Facial (VCF) syndrome], often does not become apparent until the child learns to talk or goes to school. A longer follow-up is needed to identify a possible development delay. Also, dysmorphies, indicative of a syndromal condition, can sometimes only be seen over the

years.

4. Clinical expression of additional anomalies
Many structural anomalies associated with CLA/P are variable in their type and severity. It is often a clinical diagnosis and will therefore depend on a subjective assessment, which differs between different researchers.

5. Knowledge and technology of indicating syndromes
The technology to identify chromosomal and structural anomalies is constantly evolving. The definition of many syndromes is also changing (there are many examples of misclassification).

6. Patient selection
Manner of collecting data and size of study population (sample size); a lot of research takes place in tertiary centers, while some of children with CLA/P are born in small clinics. The prevalence of CLA/P will be underestimated this way. In addition, a large population should be included, as CLA/P is a rare condition.

7. Study population and time variation
The prevalence of CLA/P is variable among different populations. Variation of prevalence over time is for example caused by reduced neonatal mortality.

B: Literature review by the working group:
In addition to previous literature, a number of methodologically difficult aspects have been identified by the working group which makes it difficult to reach a general conclusion. These points are as follows:

1. Population
In the studies, the additional anomalies were often classified differently and there was a difference in the classification of possible categories of CLA/P (CL and CL/P or CLP and CP).
The definition of median cleft is often not clear. Median cleft often lacks additional information to properly classify the CLA/P. Median cleft was not included in the postnatal CLA/P studies. These cases have been or excluded from the study (as in Walker et al. 2001) or did not occur in the postnatal population (fetal death high or possibly included in the CL/P group).

2. Prenatal and postnatal
There are major differences between prenatal and postnatal studies. The percentage of prenatally detected additional anomalies in CLA/P is expected to be higher than the percentage of additional postnatal anomalies. This is explained by the natural and iatrogenic selection made prenatally. CLA/P is common in severe chromosome aberrations or genetic syndromes. It is precisely those pregnancies, which often end up in miscarriage or intrauterine death, or which are terminated based on the findings. In addition, a fetus with an associated CL ± P will be detected earlier

than a fetus with an isolated CL ± P. Although a CP is more commonly associated with additional anomalies, a CP is often only detected prenatally in the presence of a retro or micrognathia.

3. Presence and severity of associated abnormality

Often, only the presence or absence of an associated disease or chromosome abnormality is considered. In many studies, it is not clear to what extent additional anomalies are present at chromosome aberration and whether they are also included in the category of additional anomalies.

Therefore, it cannot be established whether the risk of chromosomal aberration is related to the presence of additional anomalies.

In no way has the severity of the abnormality or consequences of the concomitant condition or abnormality been described in these studies for child, family or parents. For example, a palatoCLA/P as part of a Pierre Robin sequence falls into the category palatoCLA/P with additional abnormalities. These abnormalities (reclining lower jaw and glossoptosis) often correct themselves spontaneously and are surgically well treatable in severe cases. The overall prognosis is good. We want to indicate that it is still possible to identify the severity and prognosis of the associated congenital anomalies in these studies. This is a complicating factor in providing this data to parents in the prenatal counseling trajectory.

4. Diagnostics

A precise overview of the established chromosomal aberrations and non-chromosomal syndromes was not always provided. It appears that trisomy 13 and 18 (more at CL/P) and the Pierre Robin (more at CP) are most commonly diagnosed. This is also reflected in the data from the NVSCA (see Table 1 in evidence tables). It should be noted that the definition for Pierre-Robin is not clear in the literature, and different criteria are used (Breugem CC, Mink van der Molen AB 2008).

When an overview of the chromosome aberrations is given, it appears that some of these chromosomal aberrations are gender chromosomal aberrations, which can be considered a random finding.

5. Research techniques

In the 1980s FISH became available for routine cytogenetic laboratories, an extension of the ability to detect small chromosomal aberrations (Cremer et al. 1988, Hopman et al. 1986). The introduction of the FISH technique allows specific micro-deletions to be identified as the cause of CLA/P. In 1991, FISH study of a 4p16 deletion consistent with Wolf-Hirschhorn syndrome in which CLA/P may be one of the symptoms, was described. In 1993 FISH 22q11 became available to determine a 22q11 deletion.2 consistent with VCF syndrome (Altherr et al. 1991, Desmaze et al. 1993). In recent years, array comparative genomic hybridization (array-CGH) research has been implemented in patient care. Array-CGH is a high-resolution screening technique that can detect micro-deletions and micro-duplications across genomes (Shinawi and Cheung 2008). An increasing number of syndromes can also be genetically proven, including the Van der Woude syndrome. It is often not mentioned that these techniques have been applied or have not yet been available. It is therefore not currently clear how large the percentage of deviations will be in the application of these techniques in prenatal and postnatal diagnosis.

Genetic research techniques

In recent years, several new techniques have been introduced that can also detect chromosomal microdeletion images and confirm syndromal images, including array-CGH research.

Osoegawa et al. (2008) Investigated 187 CLA/P patients with array CGH studies; (20 patients with Van der Woude syndrome or lippits; 63 syndromal CLA/P patients and 104 non-syndromal CLA/Pisses). A total of nine patients (5%) detected a microdeletion (6 of the old patients; one syndromal CLA/P, 22q11 deletion; two non-syndromal CLA/P).

22q11 deletion/VeloCardioFacial syndrome

VeloCardioFacial (VCF)/22q11 deletion syndrome appears to be a frequent cause of CLA/P. Targeted research by Bashir et al. (2008) Nine (6 submucous CP, 2 CP, 1 unilateral CLP) out of 134 CLA/P patients (7%) with FISH study showed a 22q11 deletion. A total of 191 CLA/P patients (13 bilateral CLP, 2 median CLA/P, 77 CP, 44 unilateral CL, 47 unilateral CLP, eight submucous CP) included in the study. It should be noted that a 22q11 deletion was observed especially in the submucous CLA/P category. A category that will not be determined prenatally.

Sivertsen et al. (2007), using MLPA studies, detected a 22q11 deletion in 1.8% (3/170) of CP patients. These three patients with 22q11 deletion all had cardiac abnormalities. In the group CP with an associated cardiac abnormality, one in three had a deletion.

In the NVSCA registration, 1.8% (23/1254) of CP have a 22q11 deletion and 0.2% (1/441) of bilateral CLP. The percentage of deletion 22q11 was 2.4% for CP with additional anomalies (11/453) and 1.6% for isolated CP (13/801).

Although VCF syndrome is particularly associated with CP, experience has shown that CL/P may also occur with 22q11 deletion. Ryan et al. (1997) In a population of 496 VCF patients, four patients (0.8%) with CL/P (2 bilateral CLP, 2 CL) were found.

In the NVSCA registration, one patient with a 22q11 deletion had a bilateral CLP (4.2% (1/24).

Search and select

A literature search was performed to determine the percentage of additional anomalies and chromosomal aberrations in prenatally established CLA/P. A total of four studies (Bergé et al. 2001, Nyberg et al. 1995, Offerdal et al. 2008, Perrotin et al. 2001) were found that carefully examined the relationship between prenatal CLA/P, associated anomalies and chromosomal aberrations. These studies are discussed.

A literature search has also been performed on the possibility of additional anomalies in postnatally established CLA/P. This resulted in a total of 1145 studies in PUBMED and 1292 studies in EMBASE Following the application of defined inclusion and exclusion criteria, eight appropriate studies (see Schedule 1 under search report) could be selected. Two studies could be added. Finally, a recent article is attached. A total of 11 studies are discussed.

The search terms of both searches can be found under search report.

Reporting

Last reviewed: 12-01-2011 Last

authorized: 12-01-2011

For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html..

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Additional prenatal genetic studies in relation to prenatal counseling in CLA/P

Primary question

When is the pregnant woman eligible for additional genetic testing if a CLA/P has been diagnosed in the child prenatally?

Recommendation

It should be concluded that there are currently no suitable studies directly from which the recommendation on additional genetic testing in prenatal CLA/P can be derived. The recommendation is based on the available literature in combination with the considerations described and is at expert opinion level. In view of this, the working group recommends that:

In prenatal CLA/P, a good family history should be obtained, aimed at identifying possible teratogenic causes of CLA/P, and a chromosome aberration or syndromal disorder within the family, of which CLA/P may be part.

In prenatal established *CL without* **associated anomalies**, invasive diagnosis is not indicated, but should be provided.

In prenatal-diagnosed *CLP without* **associated anomalies**, caution with regard to invasive diagnosis is advised. The possibility of prenatal cytogenetic or molecular genetic diagnosis should be discussed.

In prenatal-determined *CP*, prenatal cytogenetic or molecular genetic diagnosis where a deletion of 22q11 can be detected is indicated. A clinical geneticist has to be consulted.

Prenatal *median cleft* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Research should be sought with a short results period.

In prenatal *median cleft*, the GEO should focus on the presence of hypertelorism, hypotelorism, microcephalhaly, holoprosencephalie, frontal/basal encephalocele and corpus callosum agenesis.

Prenatally diagnosed *CLA/P with associated anomalies* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Multidisciplinary consultations (including gynecology, clinical genetics, clinical cytogenetics, pediatrician and plastic surgeon) should be conducted.
Research should be sought with a short results period.

If a *mandibula hypoplasia* is detected, a clinical geneticist should be consulted.

Scientific studies should be conducted in the Dutch population to investigate the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P, with good and long-term follow-up of these patients. For this, a good national register, with both prenatal and postnatal data recorded in a database, is essential.

This will also include consideration of whether (targeted) array CGH or MLPA are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

The results of this study are of great importance in order to adjust the recommendations for additional diagnosis in prenatally-established CLA/P to accurate and suitable data.

Considerations

1. Considerations by category of CLA/P

The additional prenatal diagnosis depends on the CLA/P category, whether or not associated anomalies are present and the gestational period (before and after 24 weeks).
The risk of chromosomal aberration in isolated CL and CLP is low. Literature has shown that CLP prenatally can be incorrectly classified as CL and associated abnormalities are not always detected. In some cases with an isolated CLP, chromosome aberration was found. Invasive prenatal diagnosis should always be offered, but is significantly less indicated in the isolated CLA/P than in an associated CLA/P. This nuance should be taken into account when counseling patients. It may be considered that if isolated CL and CLP are detected after 24 weeks of gestation, karyotyping should not occur unless there is a strong suspicion of chromosome abnormality and this information is relevant for further treatment.
Since median cleft is never isolated, prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist is required. Median CLA/P may be a phenomenon of chromosome aberration, including trisomy 13 and syndromal aberrations, including holoprosencephaly spectrum.
The highest percentage of additional anomalies and chromosome aberrations is found in CP. Chromosome aberration was often a 22q11 deletion. The determination of this deletion requires targeted additional genetic research.
Mandibulo hypoplasia may be an indication of a specific syndromic diagnosis. If a mandibula hypoplasia is detected, a clinical geneticist should be consulted.

2. Risk of the procedure

Of course, the indication of invasive diagnosis must always weigh the risk of the procedure against the importance of diagnosing. The risk of loss of pregnancy due to amniotic fluid puncture is approximately 0.3% (NVOG Guideline for Prenatal Diagnosis).

3. Scientific research and follow-up

Scientific research and follow-up on the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P is of great importance in order to adapt the recommendations on additional diagnosis in prenatal CLA/P in the future to appropriate

techniques and correct data. The occurrence of postnatally-associated abnormalities following a prenatally-suspected isolated CLA/P is especially interesting. For this, a good national register is essential, with both **prenatal** and **postnatal** data recorded in a database.

This will also include consideration of whether (targeted) array CGH or MLPA studies are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

Substantiation Conclusions

Level 2	There is evidence that the rate of additional anomalies in **prenatally** determined schisis is higher than in postnatally determined schisis by 0-20% in CL, 24-52% in unilateral CLP, 48-79% in bilateral CLP, 100% in CP and 100% in median cleft. *B: Bergé et al. (2001), Perrotin et al. (2001), Nyberg et al. (1995)*

Level 2	There is evidence that the percentage of chromosomal aberrations in **prenatal** schisis is related to the presence or absence of additional aberrations. In isolated schisis, the percentage of chromosomal aberrations is 0-11% (1/9)[8], in schisis with associated aberrations, the percentage of chromosomal aberrations varies between 0-100% in the different studies. *B: Bergé et al. (2001), Perrotin et al. (2001), Nyberg et al. (1995)*

Level 2	There is evidence that the rate of chromosomal aberrations in **prenatally** determined isolated schisis varies by category and is 0% in CL, CL/P or CLP 0-11% (1/9)[8]. *B: Bergé et al. (2001), Perrotin et al. (2001), Nyberg et al. (1995)*

Level 2	There is evidence that the percentage of chromosomal aberration in **prenatal** schisis established **with additional anomalies** is higher than in postnatally established schisis with additional anomalies, and in: • Unilateral CLP with associated deviations 33-67%; • bilateral CLP with associated deviations 54-76%; CP with • associated deviations 100% (2/2)[7]; • median cleft with associated abnormalities 61-82%. *B: Bergé et al. (2001), Perrotin et al. (2001), Nyberg et al.*

Summary of literature

Discussion of literature; prenatal

There were only four studies (Bergé et al. 2001, Nyberg et al. 1995, Offerdal et al. 2008, Perrotin et al. 2001) were found that carefully examined the relationship between prenatal CLA/P, associated anomalies and chromosomal aberrations. Several studies were excluded for the following reasons: (I) the absence of genetic diagnosis in the study population (including karyotytyping), (ii) non-Caucasian study population, due to the varying prevalence of CLA/P in the different population groups, (iii) published before 1995, due to the availability of genetic research techniques.
Nyberg et al. (1995), Bergé et al. (2001) and Perrotin et al. (2001) investigated resp. 65, 70 and 62 fetuses with CL ± P, median cleft and CP.
For these studies, they were conducted in a tertiary center, i.e. in a selected population. A large number of fetuses were karyotyped without specific additional cytogenetic testing, including FISH or DNA diagnostics.
The results are summarized in Table 1.

In a recent study by Offerdal et al. (2008) 101 fetuses and neonates with CL ± P and CP were examined, in which at least one prenatal ultrasound examination was performed.
The results of the studies are discussed using the different categories of CLA/P, which show both the percentages of additional anomalies and chromosome aberrations per CLA/P category. Chromosome aberration rates for insulated and granulated CLA/P are also presented with additional anomalies per CLA/P category (see also Table 1 and the extended table (evidence tables)).

Table 1: Additional anomalies and chromosomal aberrations in prenatally detected CLA/P, by CLA/P category - in percentage and (numbers). Comprehensive table - see evidence tables.

Prenatal				
	Additional anomalies (%) - inc. fetuses with chrom. defect	Chromosomal deviations (%)	Chromosomal chromosomal aberrations deviations in insulated CLA/P	CLA/P with additional anomalies
Non-midline	0% (0/3) ([7]) to 20% (1 /5) ([8])	0% (0/5) ([8]) 0% (0/2#) ([7])	0% (0/4) ([8]) 0% (0/2#) ([7])	0% (0/1) ([8])
CL Unilateral 24% (7/29) ([9])** to 52% (13/25) ([7]) CLP		14% (4/29?) ([9])** up to 38% (8/21#) ([7])	0% (0/22) ([9])** up to 11% (1/9) ([8])	8 7 33% (2/6) ( ) to 67% (8/12#) ( )
Bilateral CLP CP	48% (13/27) ([9])** to 79% (22/28‡) ([7]) 100% (2/2) ([7])	30% (6/20) ([8]) to 63%* (17/27#) ([7]) 100% (2/2) ([7])	0% (0/9) ([8]) 0% (0/14) ([9])** - (0/0) ([7-8-9])	54% (7/13) (9)** to 76%* (16/21#) ([7]) 100% (2/2) ([7])
Median Cleft	100% (21/12) ([8])	61%* (11/18#) ([8]) up to 82%* (9/11) ([7])	- (0/0) ([7-8-9])	61%* (11/18#) ([8]) to 82%* (9/11) ([7])

* All had additional anomalies, ** CL/P, # karyotyped, ‡ of 1 case data additional anomalies not available

Additional anomalies in prenatally established CLA/P

Additional anomalies were observed more frequently in prenatally determined unilateral and bilateral CLP than in CL. With prenatally median cleft, associated abnormalities has always detected.

The percentage of prenatally detected additional anomalies in:

- Cleft lip (CL): 0 % (0/3) 7 to 20 % (1/5)[8]
  The anomaly included cardiac abnormality and situs inversus.

- Cleft lip and palate (CLP):
  - Unilateral: 24% (7/29 CL/P)[9] to 52% (13/25)[7] Bilateral:
  - 48% (13/27 CL/P)[9] to 79% (22/28)[7]
- Cleft palate (CP):
  Cleft palate without clept lip has rarely been diagnosed prenatally. In the Bergé study, 2 fetuses were detected with CP. Both had associated anomalies.

- Median Cleft: All fetuses with a median cleft ((11/11)[7];(21/21)[8]) had associated anomalies, especially cerebral implant disorders.

Chromosome aberrations in prenatal CLA/P.

Prenatally established unilateral and bilateral CLP were more frequently related to chromosomal aberrations than CL. Median cleft has the highest percentage of chromosome aberrations.

The percentage of prenatal chromosomal aberrations was in:

- CL: 0% (0/5 [8]; 0/2 [7])
- Unilateral CLP: 14% to 38% (4/29 CL/P [9]; 8/21 [7])
- Bilateral CLP: 30% to 63% (6/20 [8]; 17/27 [8])
- Median cleft: 61% to 82% (11/18 [8]; 9/11 [7])

The highest percentage of chromosomal aberrations was found in median cleft fetuses. The most common

chromosome aberrations were:

- trisomy 13 (30-44%)
- trisomy 18 (5-19%).

Anomalies were found in all fetuses with trisomy 13 or 18 in the prenatal ultrasound study. In the majority of fetuses with median cleft, cerebral application disorders were observed.
As mentioned, Offerdal et al. investigated (2008) 101 fetuses and neonates with CL ± P and CP, in which at least one prenatal ultrasound examination was performed.
In the study of Offerdal et al. (2008) 31 (31%) fetuses were karyotyped prenatally; chromosome abnormality was detected in 12% (12/101) of the fetuses/neonates.
In 9 out of 12 chromosome aberrations, there were ultrasound findings and prenatal chromosome aberration was observed. 3 of the 12 chromosome aberrations were observed post-natally.
The percentage of chromosomal aberrations was 10% (8/77) in CL/P and 17% (4/24) in CP. No chromosome abnormality was detected in CL.

Chromosome aberrations in prenatally presumed isolated CLA/P:

The risk of chromosomal aberration in prenatal isolated schisis is low.

The percentage of chromosomal aberrations was in:

- Isolated CL: 0% (0/4 [8]; 0/2 [7])
- Isolated unilateral CLP: 0% to 11% (0/22 CL/P [9]; 1/9 [8]) Isolated
- bilateral CLP: 0% (0/9 [8]; 0/14 CL/P) [9] **)

In Bergé et al. (2001) and Perrotin et al. (2001) and 76% (16/21) and 39% (14/36) of the fetuses with a presumed isolated CLA/P was karyotyped. No chromosome abnormalities were observed in either study.
Nyberg et al. (1995) described 9 fetuses with an isolated unilateral CLP of which a mosaic trisomy 22 was detected in 1 case.

Chromosome aberrations in fetuses with CLA/P and additional anomalies:

The risk of chromosomal aberration in prenatally established schisis is higher if there are additional anomalies and is related to the schisis category. In particular for the CLP category, the risk of chromosome aberration increases if there are additional anomalies.

The percentage of chromosomal aberrations was in:

- CL with additional anomalies: 0% (0/1)[8]
- Unilateral CLP with additional anomalies: 33% to 67% (2/6 [8]; 8/12 [7])
- Bilateral CLP with additional anomalies: 54% to 76% (7/13 Cl/P [9]; 16/21 [7])
- Median cleft with additional anomalies: 61% to 82% (11/18 [8]; 9/11 [7])

Almost all fetuses with chromosome aberration (19/208; 35*f*357) had additional anomalies. In the study of Offerdal et al. (2008) ultrasound aberrations were seen in 9 out of 12 fetuses (75%) with chromosome abnormality.

Mortality
CLP and median cleft were associated with higher mortality (resp. 33% (5/15) in unilateral CLP, 50% (10/20) in bilateral CLP and 100% (21/21) in median cleft), then in CL (20% (1/5)[8].

Search and select

A literature search was performed to determine the percentage of additional anomalies and chromosomal aberrations in prenatally established CLA/P. A total of four studies (Bergé et al. 2001, Nyberg et al. 1995, Offerdal et al. 2008, Perrotin et al. 2001) were found that carefully examined the relationship between prenatal CLA/P, associated anomalies and chromosomal aberrations. These studies are discussed.

A literature search has also been performed on the possibility of additional anomalies in postnatally established CLA/P. This resulted in a total of 1145 studies in PUBMED and 1292 studies in EMBASE Following the application of defined inclusion and exclusion criteria, eight appropriate studies (see Schedule 1 under search report) could be selected. Two studies could be added. Finally, a recent article is attached. A total of 11 studies are discussed.
The search terms of both searches can be found under search report.

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database
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Additional post-natal genetic studies in the prenatal counseling of CLA/P

Primary question

When is the pregnant woman eligible for additional genetic testing if a CLA/P has been diagnosed in the child prenatally?

Recommendation

It should be concluded that there are currently no suitable studies from which the recommendation on additional genetic testing in prenatal CLA/P can be derived directly. The recommendation is based on the available literature in combination with the considerations described and is at expert opinion level. In view of this, the working group recommends that:

In prenatal CLA/P, a good family history should be obtained, aimed at identifying possible teratogenic causes of CLA/P, and a chromosome aberration or syndromal disorder within the family, of which CLA/P may be part.

In prenatal established *CL without* **associated anomalies**, invasive diagnosis is not indicated, but should be provided.

In prenatal-diagnosed *CLP without* **associated anomalies**, caution with regard to invasive diagnosis is advised. The possibility of prenatal cytogenetic or molecular genetic diagnosis should be discussed.

In prenatal-determined *CP*, prenatal cytogenetic or molecular genetic diagnosis where a 22q11 deletion can be detected is indicated. A clinical geneticist has to be consulted.

Prenatal *median cleft* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Research should be sought with a short results period.

In prenatal *median cleft*, the GUO should focus on the presence of hypertelorism, hypotelorism, microcephalhaly, holoprosencephalie, frontal/basal encephalocele and corpus callosum agenesis.

Prenatally diagnosed *CLA/P with associated anomalies* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Multidisciplinary consultations (including gynecology, clinical genetics, clinical cytogenetics, pediatrician and plastic surgeon) should be conducted.
Research should be sought with a short results period.

If a *mandibula hypoplasia* is detected, a clinical geneticist should be consulted.

Scientific studies should be conducted in the Dutch population to investigate the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P, with good and long-term follow-up of these patients. For this, a good national register, with both prenatal and postnatal data recorded in a database, is essential.

This will also include consideration of whether (targeted) array CGH or MLPA are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

The results of this study are of great importance in order to adjust the recommendations for additional diagnosis in prenatally-established CLA/P to accurate and suitable data.

Considerations

1. Considerations by category of CLA/P

The additional prenatal diagnosis depends on the CLA/P category, whether or not associated anomalies are present and the gestational period (before and after 24 weeks).
The risk of chromosomal aberration in isolated CL and CLP is low. Literature has shown that CLP prenatally can be incorrectly classified as CL and associated abnormalities are not always detected. In some cases with an isolated CLP, chromosome aberration was found. Invasive prenatal diagnosis should always be offered, but is significantly less indicated in the isolated CLA/P than in an associated CLA/P. This nuance should be taken into account when counseling patients. It may be considered that if isolated CL and CLP are detected after 24 weeks of gestation, karyotyping should not occur unless there is a strong suspicion of chromosome abnormality and this information is relevant for further treatment.
Since median cleft is never isolated, prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist is required. Median CLA/P may be a phenomenon of chromosome aberration, including trisomy 13 and syndromal aberrations, including holoprosencephaly spectrum.
The highest percentage of additional anomalies and chromosome aberrations is found in CP. Chromosome aberration was often a 22q11 deletion. The determination of this deletion requires targeted additional genetic research.
Mandibulo hypoplasia may be an indication of a specific syndromic diagnosis. If a mandibula hypoplasia is detected, a clinical geneticist should be consulted.

2. Risk of the procedure

Of course, the indication of invasive diagnosis must always outweigh the risk of the procedure against the importance of diagnosing. The risk of miscarriage due to amniotic fluid puncture is approximately 0.3% (NVOG Guideline for Prenatal Diagnosis).

3. Scientific research and follow-up

Scientific research and follow-up on the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P, is of great importance to the recommendations

concerning additional diagnosis in prenatal CLA/P in the future to be able to adapt to appropriate techniques and appropriate data. The occurrence of postnatally-associated abnormalities following a prenatally-suspected isolated CLA/P is especially interesting. For this, a good national register is essential, with both **prenatal** and **postnatal** data recorded in a database.

This will also include consideration of whether (targeted) array CGH or MLPA studies are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

Substantiation Conclusions

Level 2	The overall risk of additional anomalies in postnatally determined schisis is likely to be between 8 and 65%, with most studies reaching 20%-30%. *B: Stoll et al. (2007), Milerad et al. (1997), Calgolari et al. (2007), Vallino et al. (2006), Drushel et al. (2006), Walker et al. (2001), Deroo et al. (2003), Kallén (1996), Russell et al. (2008), Offerdal et al. (2008); Beriaghi et al. (2009)*

Level 2	The potential for additional anomalies in postnatally determined schisis is likely to vary by ICES category, with 8-12% at CL, 11-32% at CL/P or CLP, and 13-65% at CP. *B: Stoll et al. (2007), Milerad et al. (1997), Calgolari et al. (2007), Vallino et al. (2006), Drushel et al. (2006), Walker et al. (2001), Deroo et al. (2003), Kallén (1996), Russell et al. (2008), Offerdal et al. (2008); Beriaghi et al. (2009)*

Level 2	The rate of non-chromosomal aberrations in all post-natally determined schisis categories is likely to be higher than the rate of chromosomal aberrations, with most non-chromosomal aberrations not being part of a syndrome. *B: Stoll et al. (2007), Milerad et al. (1997), Calgolari et al. (2007), Vallino et al. (2006), Drushel et al. (2006), Walker et al. (2001), Deroo et al. (2003), Kallén (1996), Russell et al. (2008), Offerdal et al. (2008); Beriaghi et al. (2009)*

Level 2	The rate of chromosomal aberrations is likely to vary by post-natally determined schisis category and is 1-2% for CL/P or CLP 5-15%, and 5-26% for CP. *B: Stoll et al. (2007), Milerad et al. (1997), Calgolari et al. (2007), Vallino et al. (2006), Drushel et al. (2006), Walker et al. (2001), Deroo et al. (2003), Kallén (1996), Russell et al. (2008), Offerdal et al. (2008); Beriaghi et al. (2009)*

Summary of literature

Discussion of literature; postnatal

Eleven studies (Stoll et al. 2007, Milerad et al. 1997, Calzolari et al. 2007, Vallino et al. 2006, Drushel et al. 2006, Walker et al. 2001, Deroo et al. 2003, Kallén 1996, Russell et al. 2008, Offerdal et al. 2008, Beriaghi et al. 2009) describes the relationship between postnatally established CLA/P, associated anomalies and chromosomal aberrations. In some studies, the population consisted of both fetuses and neonates with CLA/P.

Table 2: Studies of additional anomalies and chromosomal aberrations in postnatal CLA/P

	N	N (Cleft)	Cleft incidence	CL (N, %)	CL/ P (N,%)	CP (N,%)
Stoll et al. (2007)[17]	334.262	651	1.9: 1000		390 (59.9)	261 (40.1)
Milerad et al. (1997)[14]		616	1.7:1000	163 (26.5)	214* (34.7)	239 (38.8)
Calzolari et al. (2007)[10]	5,989,834	4719	0.91:1000	1806 (38.3)	2913* (61.7)	
Vallino et al. (2006)[18]	1,140,668	2022	0.57:1000		1189 (58.8)	833 (41.2)
Drushel et al. (1996)[12]	2,159,856	2786	1.29:1000		1599* (57.4)	1187 (42.6)
Walker et al.** (2001)[19]	217.429	263	1.2:1000	84 (31.9)	179* (68.1)	
Deroo et al. (2003) [11]	298.138	502	2.04:1000		280 (55.8)	222 (44.2)
Kallén et al (1996)[13]	5,100,000	8315	1.6:1000	2029 (24.4)	3232* (38.9)	3021 (36.3)
Russell et al. (2008)[16]	108.220	225	2.1:1000		127 (56.4)	98 (43.6)
Offerdal et al. (2008)[15]	49.315	101	1.77:1000		77 (76.2)	24 (23.8)
Beriaghi et al. (2009)[20]		1127			595 (52.8)	532 (47.2)

The results by category of CLA/P are summarized in Table 3.

The percentage of chromosomal aberrations in isolated CLA/P and the percentage of chromosomal aberration in CLA/P with additional anomalies cannot be derived from the studies. They are therefore not included in the table. Median cleft has not been described in the studies. This case may have been included under CLP, which was the case with Eurocat Noord-Nederland upon request.

Table 3: Additional anomalies and chromosomal aberrations in postnatal CLA/P, by CLA/P category - in percentage and (numbers). Comprehensive table - see evidence tables.

Postnatal		
	Additional anomalies (%)	Chromosomal aberrations (%)
Non-midline CL	8% *** (13/163) ([14]) to 12% (213/1806) ([10])	1% (22/2029) ([13]) to 2% (32/1806) ([10])
Unilateral/bilateral CLP	11% (66/595) ([20]) to 32% ** (25/77) P ([15])	5% (153/2913) ([10]) to 15% ** (91/595) ([20])
CP	13% (68/532) ([20]) to 65%*** (144/222) ([11])	5% (134/2527) ([13]) to 26% (138/532) ([20])
Median Cleft		

** CL/P, *** additional anomalies (including patients with chromosome aberration) p= pre- and postnatal

Additional anomalies in postnatally established CLA/P

The presence of additional conditions in postnatally established schisis varies by category. Additional conditions are more frequently observed with CP than with CL.

The percentage of additional conditions detected was in:

- Split lip (CL): 8% (13/163)[14] to 12% (213/1806)[10]
- Split lip and/or palate (CL/P): 11 (66/595)[11] of children up to 32% of fetuses and neonates (25/77) [15]
- Cleft palate (CP): 13% (68/532)[14] to 65% (144/222)[11]

The additional conditions were more likely to include additional anomalies without abnormal karyotyping than additional anomalies associated with chromosome aberration.
An overview of the established syndromic diagnoses can be found in evidence tables.

Chromosome aberrations in postnatally established CLA/P

The percentage of chromosome aberrations in postnatally determined schisis is different by category and is higher in CL/P and CP than in CL.

The percentage of chromosome aberrations was in:

- Cleft lip (CL): 1% to 2% ((22/2029) 13; (32/ 1806)[10])
- Cleft lip and/or palate (CL/P): 5% to 15% ((153/2913[10]; (91/595) [20]) ,
- Cleft palate (CP): 5% to 26% ((134/2527[13]; 138/532) [20]) ,

The most common chromosome aberrations in the total number of children with a postnatally determined CLA/P were:

- trisomy 13 (0.5% (3/616)[14] to 2.6% (7/263) [19]),
- trisomy 18 (0.3% (2/616) [14] to 3.1% (64/2022) [18]).

Walker et al. found aneuploidy in 15 fetuses. In 1 case of bilateral CLP (6.7%), the ultrasound did not detect

any additional anomalies. The chromosome aberration is not mentioned. The percentage of aneuploidy without additional anomalies detected by ultrasound in the overall population studied was 0.4% (1/263)[19].

CL and CLP or CL/P were rarely part of a syndrome; however, a syndromic diagnosis was more frequent in CP. Pierre-Robin sequence was diagnosed fairly often in a cleft palatum without a cleft lip (CP), in Vallino et al. 14.6% (122/833).

Search and select

A literature search was performed to determine the percentage of additional anomalies and chromosomal aberrations in prenatally established CLA/P. A total of four studies (Bergé et al. 2001, Nyberg et al. 1995, Offerdal et al. 2008, Perrotin et al. 2001) were found that carefully examined the relationship between prenatal CLA/P, associated anomalies and chromosomal aberrations. These studies are discussed.

A literature search has also been performed on the possibility of additional anomalies in postnatally established CLA/P. This resulted in a total of 1,145 studies in PUBMED and 1,292 studies in EMBASE Following the application of defined inclusion and exclusion criteria, eight appropriate studies (see Schedule 1 under search report) could be selected. Two studies could be added. Finally, a recent article is attached. A total of 11 studies are discussed.
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Data Dutch CLA/P population from the NVSCA registration

Primary question

When is the pregnant woman eligible for additional genetic testing if a CLA/P has been diagnosed in the child prenatally?

Recommendation

It should be concluded that there are currently no suitable studies from which the recommendation on additional genetic testing in prenatal CLA/P can be derived directly. The recommendation is based on the available literature in combination with the considerations described and is at expert opinion level. In view of this, the working group recommends that:

In prenatal CLA/P, a good family history should be obtained, aimed at identifying possible teratogenic causes of CLA/P, and a chromosome aberration or syndromal disorder within the family, of which CLA/P may be part.

In prenatal established *CL without* **associated anomalies**, invasive diagnosis is not indicated, but should be provided.

In prenatal-diagnosed *CLP without* **associated anomalies**, caution with regard to invasive diagnosis is advised. The possibility of prenatal cytogenetic or molecular genetic diagnosis should be discussed.

In prenatal-determined *CP*, prenatal cytogenetic or molecular genetic diagnosis where a 22q11 deletion can be detected is indicated. A clinical geneticist has to be consulted.

Prenatal *median cleft* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Research should be sought with a short results period.

In prenatal *median cleft*, the GUO should focus on the presence of hypertelorism, hypotelorism, microcephalhaly, holoprosencephalie, frontal/basal encephalocele and corpus callosum agenesis.

Prenatally diagnosed *CLA/P with associated anomalies* requires prenatal cytogenetic or molecular genetic diagnosis and consultation of a clinical geneticist. Multidisciplinary consultations (including gynecology, clinical genetics, clinical cytogenetics, pediatrician and plastic surgeon) should be conducted.
Research should be sought with a short results period.

If a *mandibula hypoplasia* is detected, a clinical geneticist should be consulted.

Scientific studies should be conducted in the Dutch population to investigate the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P, with good and long-term follow-up of these patients. For this, a good national register, with both prenatal and postnatal data recorded in a database, is essential.

This will also include consideration of whether (targeted) array CGH or MLPA are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

The results of this study are of great importance in order to adjust the recommendations for additional diagnosis in prenatally-established CLA/P to accurate and suitable data.

Considerations

1. Data NVSCA (Luijsterburg and Vermeij-Keers, 1999-2008 [21]
The registration of the NVSCA is a standardized register, and very valuable (Rozendaal et al. 2010c). It should be noted that the register does not include neonatal mortality on the basis of CLA/P with or without additional anomalies. Furthermore, the register is not an 'ongoing' register. Subsequent diagnoses or additional anomalies are not recorded, this is a significant percentage (Rozendaal et al., in preparation). Chromosome studies have generally been performed as indicated.
The highest percentage of additional anomalies and chromosome aberrations is found in CP (36% and 3% respectively). A category that is not expected to be detected in the SEO.
Table 2 of the evidence tables gives an overview of the number of diagnoses included in the recording.
The most commonly used syndromic diagnoses are Pierre-Robin, VCF/deletion22q11 and Van der Woude syndrome. Stickler syndrome is also common. When detecting a mandibula hypoplasia, Pierre-Robin sequence, 22q11 deletion and Stickler syndrome should be considered.
The most common chromosome aberrations are 22q11 deletion, trisomy 21, 4p- and trisomy 13.

2. Syndromic diagnostics
CLA/P can be part of more than 600 syndromes, including chromosome aberrations and microdeletion images (about 6% of syndromic diagnosis). When diagnosing syndromic diagnosis, a good family history can be crucial.
A good family history, if necessary in consultation with a clinical geneticist, should be obtained when detecting a CLA/P. The history focuses on possible teratogenic causes of CLA/P and the determination of a familial chromosome translocation or syndromal conditions associated with CLA/P within the family.
It is also important that newborns with CLA/P are seen by a clinical geneticist for further dysmorphological examination. Based on the physical examination, targeted additional genetic diagnosis may be considered.

3. Scientific research and follow-up
Scientific research and follow-up on the occurrence of additional anomalies and/or genetic abnormalities in prenatally detected patients with CLA/P, is of great importance to the recommendations

concerning additional diagnosis in prenatal CLA/P in the future to be able to adapt to appropriate techniques and appropriate data. The occurrence of postnatally-associated abnormalities following a prenatally-suspected isolated CLA/P is especially interesting. For this, a good national register is essential, with both **prenatal** and **postnatal** data recorded in a database.

This will also include consideration of whether (targeted) array CGH or MLPA studies are suitable techniques for prenatal diagnosis in pregnancies where a CLA/P has been identified by the GUO.

Substantiation Conclusions

The percentage of additional anomalies in the Dutch schisis population is 20%.

The percentage of chromosomal aberrations in the Dutch schisis population is 1.6%.

The percentage of additional anomalies in the Dutch schisis population varies by schisis category and is 10% in CL, 13% in CLP (unilateral CLP 11%; bilateral CLP 18%), 36% in CP and 30% in median cleft.

The percentage of chromosomal aberrations in the Dutch schisis population varies by schisis category and is 0% in CL, 1.2% in CLP (unilateral CLP 0.8%; bilateral CLP 2%), 3% in CP and 2% in median cleft.

The percentage of chromosomal aberrations in the Dutch schisis population depends on the presence or absence of additional aberrations and varies by category. In isolated schisis, the percentage of chromosomal aberrations in CL is 0%, in unilateral CLP is 0.2%, in bilateral CLP is 0.5%, in CP is 3% and in median cleft is 3%, For schisis with associated aberrations, the percentage of chromosomal aberrations is 0% in CL, 6% in unilateral CLP, 9% in bilateral CLP, 5% in CP and 7% in median cleft.

The highest percentage of chromosome aberrations (9%) is found in the bilateral CLP category with additional anomalies.

No chromosome aberrations have been recorded in category CL.

The percentage of 22q11 deletion is 0.6% in the Dutch schisis population. For CP, this percentage is 1.8%.

Summary of literature

Data Dutch CLA/P population from the NVSCA register

Almost all patients with a CLA/P are treated in the Netherlands by one of the 14 CLA/P teams. On the patient's first visit to a CLA/P team, the visit is recorded anonymously. The registration forms are then sent to the register and, after verification and any supplementation of the data, are recorded in the database. Each year, the number of patients registered by the respective teams is checked and an annual register is issued. This registration is managed by the Dutch Association for CLA/P and Craniofacial Abnormalities (NVSCA).

The registration is standardized by means of a registration form developed by the NVSCA (Luijsterberg and Vermeij-Keers 1999). This form describes the craniofacial abnormalities including CLA/P in topographic and morphological detail. The NVSCA register has been validated (Rozendaal et al. 2010a, 2010b). In addition to general data, the presence of additional anomalies per organ system, chromosome aberrations and syndromic diagnosis are also recorded. The NVSCA register has been fully digitized since 01/01/2008. Registration of prenatal diagnosis of CLA/P via the CLA/P teams also started from 01/01/2008.
It is important to note that the registration of the patient has often not (yet) been performed a clinical genetic study and is not an on-going register. Therefore, any diagnosis established after registration is not included in the register. Validation research of this part of the registration shows that a significant percentage of the diagnostics are missing (Rozendaal et al., in preparation).
Table 4 below shows the percentages of additional anomalies, chromosomal aberrations and syndromic diagnoses per CLA/P category from the NVSCA register for the years 1997 to 2007 (Luijsterburg and Vermeij-Keers, 1999-2008). It should be noted that the dates of the NVSCA include adopted children (n=157; 48 non midline CLA, 51 unilateral CLP, 30 bilateral CLP and 28 CP). Within these CLA/P groups, n=2 syndromic diagnoses have been made, namely: Pierre Robin (CP), EEC (bilateral CLP) and n=2 chromosome aberrations: 22q11 deletion (unilateral CLP and CP). The adopted children are not listed in the table.
The table includes 47 cases with a midline CL. These are cases with hypo- and hypertelorism, according to holoprosencephalie cases and the cases with median cleft face syndrome and, of course, cases without specific general diagnosis.
Median Cleft with hypotelorism (cyclopes/holoprosencephaly series) and hypertelorism (synonyms: median cleft face syndrome/frontonasal dysplasia/bifid nose with median cleft lip) respectively were not included in the NVSCA CLA/P register annual reports. These are craniofacial abnormalities that have a different pathogenesis than CLA/P, often associated with brain abnormalities and therefore are included in the register of craniofacial abnormalities of the NVSCA. The median cleft data is obtained from this record.

Table 4: Additional anomalies and chromosomal aberrations in CLA/P patients at the first visit to a CLA/P team included in the NVSCA register, by CLA/P category — in percentages and (numbers).

CLA/P category	Additional anomalies (head/ neck or other systems)	Chromosomal aberrations	Chromosomal aberrations in isolated CLA/P	Chromosomal aberrations in CLA/P with additional anomalies	Syndromes (excl alagille and pompe)	Syndromes in isolated ischio	SYN at s with goo d ano
Non-midline CL (n=1018)	10% (102)	0% (0)	0% (0)	0% (0)	1% (11)	0.2% (2)	9% (
Unilateral CLP (n=964)	11% (103)	0.8% (8)	0.2% (2)	6% (6)	2% (18)	0.8% (7)	11%
Bilateral CLP (n=441)	18% (81)	2% (9)	0.5% (2)	9% (7)	2% (11)	1% (4)	9% (
CP (n=1254)	36% (453)	3% (42)	3% (23)	5% (24)	22% (271)	6% (46)	50%
Median Cleft (n=47)	30% (14)	2% (1)	3% (1)	7% (1)	9% (4)	3% (1)	21%

Additional anomalies in CLA/P in NVSCA register:

The percentage of additional anomalies in the Dutch schisis population varies by category, with the percentage being lowest in CL and highest in CP.

The percentages shall be expressed:

- Non midline CL 10%
- Unilateral CLP 11%
- Bilateral CLP 18%
- CP 36%
- Median Cleft 30%

Chromosome aberrations in CLA/P in NVSCA register:

The percentage of chromosome aberrations in the Dutch schisis population varies by category, with the percentage being highest in CP.
No chromosome aberrations have been described in CL.

The percentages shall be expressed:

- Non midline CL 0%
- Unilateral CLP 0.8%
- Bilateral CLP 2%
- CP 3%
- Median Cleft 2%

Of the CP patients, 24/1254 (2%) had a 22q11 deletion.

Chromosomal aberration in insulated CLA/P in NVSCA register:

The percentage of chromosome aberrations in the Dutch isolated schisis population varies by category, with the percentage being highest in CP and median cleft. No chromosome aberrations have been described in isolated CL.

No chromosome aberrations have been recorded in isolated CL.
The majority of chromosome aberrations in isolated CLA/P are registered in the categories Median Cleft (3%) and CP (3%).

Of the isolated CLP, 0.3% (0.2% for unilateral CLP, 0.5% for bilateral CLP) have chromosome aberration.
This involved a total of 4 patients (2x trisomy 21 (1x unilateral CLP, 1x bilateral CLP), 1x trisomy 18 (bilateral CLP), 1x 4p/Wolf-Hirschhorn (unilateral CLP).

Of the isolated midline CL, 1 patient (3%) had chromosome aberration.
This may be based on the fact that additional derogations exist but have not been registered.

3 % (23/801) of the isolated CP has chromosome aberration. 13 out of 23 (56%) had a 22q11 deletion.

Chromosome aberration in CLA/P with additional anomalies in NVSCA register:

The percentage of chromosome aberrations in the Dutch schisis population is higher in the presence of additional aberrations and varies by category. The percentage is highest in bilateral CLP with additional anomalies. Chromosome aberrations have not been described in CL with additional anomalies.

As also shown in the literature, the percentage of chromosome aberration is higher if there are additional anomalies besides the CLA/P.

The percentage of chromosomal aberrations was in:

- Non midline CL with additional anomalies 0%
- Unilateral CLP with additional anomalies 6%
- Bilateral CLP with additional anomalies 9%
- CP with additional anomalies 5%
- Median Cleft with additional anomalies 7%

Syndromic diagnoses and abnormal karyotypes in NVSCA register:

The most common diagnoses in the Dutch schisis population are Pierre Robin sequence, Van der Woude syndrome and Stickler syndrome.

The most common diagnoses are Pierre Robin sequence, Van der Woude and Stickler syndrome. The number of syndromic diagnoses identified is also related to the CLA/P category and the presence or absence of additional anomalies.
Most syndromic diagnoses are made in the category CP with additional anomalies and amounts to 50%. In this category, the diagnosis was Pierre Robin 216 times (n=1254) of which 38 cases were without mandibula hypoplasia. In addition, a mandible hypoplasia was scored in 43 patients without a diagnosis of Pierre Robin. This shows, as mentioned above (see B point 4), that the definition for Pierre-Robin is not only unambiguous in literature but also in practice, and different criteria are used (Breugem CC, Mink van der Molen AB 2008).

In isolated non midline CL, only 0.2% of syndromes are diagnosed.
The syndromic diagnoses and abnormal karyotypes included in the registration are shown in Table 2 (see evidence tables).

CLA/P and 22q11 deletion in NVSCA register:

The percentage of 22q11 deletion is 0.6% in the Dutch schisis population. For CP this percentage is 1.8%, and for CLP it is 0.2%.

The register included 24 patients (24/3724) (23 CP; 1 bilateral CLP) with a 22q11 deletion. 1.8
% (23/ 1254) of CP had a 22q11 deletion and 0.2% (1/441) of bilateral CLP.
In 46% (11/24) of CP patients with a 22q11 deletion there were additional anomalies. The percentage of

22q11 deletion was for:

- CP with additional anomalies 2.4% (11/ 453)
- Isolated CP 1.6% (13/801)

Summary data of the Dutch CLA/P population from the NVSCA register:
According to the NVSCA register, additional anomalies occur in 20% of the Dutch CLA/P population. Chromosomal abnormality was identified in 1.6%. It should be noted that the register does not include neonatal mortality based on CLA/P with or without additional anomalies.
The percentage of additional anomalies and chromosome aberrations varies by CLA/P category. The highest percentage of additional anomalies and chromosome aberrations is found in CP (36% and 3% respectively).
No chromosome aberrations were recorded in the category non-midline CL.
The percentage of chromosome aberrations and syndromic diagnosis is related to the presence of additional anomalies.
The most registered syndromic diagnoses are Pierre Robin, Van der Woude and Stickler syndrome.

Search and select

A literature search was performed to determine the percentage of additional anomalies and chromosomal aberrations in prenatally established CLA/P. A total of four studies (Bergé et al. 2001, Nyberg et al. 1995, Offerdal et al. 2008, Perrotin et al. 2001) were found that carefully examined the relationship between prenatal CLA/P, associated anomalies and chromosomal aberrations. These studies are discussed.

A literature search has also been performed on the possibility of additional anomalies in postnatally established CLA/P. This resulted in a total of 1,145 studies in PUBMED and 1,292 studies in EMBASE Following the application of defined inclusion and exclusion criteria, eight appropriate studies (see Schedule 1 under search report) could be selected. Two studies could be added. Finally, a recent article is attached. A total of 11 studies are discussed.
The search terms of both searches can be found under search report.

Reporting

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For full reports, evidence tables and any related products, please refer to the Guideline database
https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html..

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Counseling in CLA/P in a prenatal diagnostic center

Parents have - after being diagnosed with a CLA/P after performing an ultrasound - several reasons to worry about the future of their child. The aim of prenatal counseling should therefore be to provide parents with unambiguous information about possible opportunities and consequences for their child. Prenatal counseling should address both psychosocial and medical issues. If the diagnosis is made before the 24th week of pregnancy, there is the possibility for parents - weighing all the information - to opt for abortion. Parents must then consider where the partus will take place.

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Experience by parents in diagnosis of CLA/P

Primary question

How is the diagnosis of CLA/P experienced by parents?

Recommendation

Prenatal diagnosis should be seen as a process in which the provision of (medical) information and professional psychosocial care plays an important role. Prenatal counseling should aim to provide parents with unambiguous information about what is possible for their child so that he/she can grow up as normally as possible. In order to achieve this goal, it is recommended that the counseling is performed by 2 persons, namely a medical professional and a psychosocial professional.

Psychosocial counseling of parents, who expect a child with a CLA/P, should be an integral part of the guidance of parents by the CLA/P team. In any case, the following issues should be addressed:

- Disappointment; Possible
- guilt;
- Impact on the family;
- How to deal with reactions from the environment;
- Intellectual development of the child; Psychosocial
- development (resilience e.g.);
- Whether or not it is possible to breast-feed (guilt);
- Possibility to give birth at home;
- Offer contact with other parents in the same position.

It is preferable that the verbal information given should be accompanied by written information.

Every CLA/P team should have a psychologist or social worker, who is adequately trained in acceptance problems, grief processing and system problems in combination with CLA/P, who is available/reachable at least five days a week during business hours for this purpose.

It is recommended that parents be offered follow-up calls where, if desired, acceptance issues (including in the family context) and attention to grief processing can be addressed.

Considerations

Based on the literature studies, it can be concluded that counseling after prenatal diagnosis of CLA/P by specialist responders is highly desirable. Parents need both information and support in the processing of the diagnosis of CLA/P. Although the literature does not clearly indicate

which discipline must provide this counseling, it is obvious that psychosocial aspects of the treatment and support of parents in acceptance and (grief) processing are provided by a trained psychologist or social worker of the CLA/P team. Two team members must preferably provide the counseling, where on the one hand there should be direct knowledge of the (surgical) treatment, and on the other hand, sufficient knowledge of the psychosocial aspects of having a child with a CLA/P should also be available (Also refer to the “Requirements of the CLA/P team” module”). This is all the more true if there are considerations relating to pregnancy termination. Counseling by two members also reduces the risk of bias in the provision of information. There should always be an opportunity to meet the other members of the team. Each imaging team is expected to anonymously record the ultrasound findings in the NVSCA register Prenatal Diagnostics (see 'NVSCA register' module and last recommendation in that module).
The opinions of the parents from the focus groups support these findings (see relatives). Due to barriers in the financial system, inter alia, distribution problems in the hospital, psychosocial care is not sufficiently guaranteed in the Dutch situation for all CLA/P teams.

Substantiation Conclusions

Level 3	The diagnosis of schisis evokes emotions among many parents such as shock, denial, sadness, anger and fear. *C: Berk et al.1999, Davalbhakt & Hall (2000), Young et al. (2001), Strauss (2002), Beaumont (2006), Murray et al. (2008), Nusbaum et al. (2008),* *D: Heineman-de Boer & Swanenburg de Veye (2010)*

Level 3	The processing of the disappointment of a prenatally established schisis by the parents can be considered as going through a grieving process. *C: Young et al. (2001), Rey-Bellet & Hohlfeld (2004)*

Summary of literature

More and more ultrasounds are performed during pregnancy, and technological improvements, among other things, to the ultrasound equipment, have led to a steady increase in the number of children who have been diagnosed with CLA/P before birth. While for the prenatal caregiver there will be a clear distinction between a first ‘term ultrasound’ and the SEO, for many parents an ultrasound is primarily an opportunity to see their child before birth.
Jones (2002) notes in this respect that the pregnant woman and her partner often do not sufficiently realize that the sonographer may find a congenital anomaly. They therefore hardly dwell on what the consequences of a different finding might be.
For many parents, the diagnosis of a child with a congenital anomaly such as a CLA/P comes as a thunder in clear sky. In the literature, reactions of the parents to the birth of a child with CLA/P are described by several authors (Davalbhakta & Hall (2000), Young et al. (2001), Strauss

(2002), Beaumont (2006), Murray et al. (2008), Nusbaum et al. (2008), Heineman-de Boer & Swanenburg de Veye (2010). They describe these reactions as feelings of shock, denial, sadness, anger, fear of the future and fear that the suture process with the baby will not go well. During the process of accepting the CLA/P, the parents go through a multitude of feelings. Rey-Bellet & Hohlfeld (2004) note that discovering every congenital anomaly causes shock and disappointment. They describe it as the beginning of a grieving process that is necessary for the acceptance of a child that is 'different'. Young et al. (2001) described the process as follows, "The mother must mourn the loss of her expected normal infant and in addition she must become attached to her actual living damaged child".
In this process of acceptance, after the birth of the baby, parents will also experience reactions from others in their social environment from the outset if the condition is visible as with a CLA/P of the lip/jaw. Strauss (2002) suspects that the final reactions to a prenatal diagnosis may be very different. Some parents will accept the abnormality and make a strong case for the best possible care and treatment while others will see the abnormality as a potential burden or fear that the child will ultimately not have a high quality of life.
In the study of Nusbaum et al. (2008) in-depth interviews compared experiences of parents who had had prenatal diagnosis and counseling (n=12) with those who had had postnatal diagnosis and counseling (n=8). All 20 parents reported a shock response when hearing the diagnosis and needed counseling from professional responders.
In the study of Rey-Bellet & Hohlfeld (2004) only included parents who received the diagnosis of their child prenatally. Twenty-nine couples completed a questionnaire. The study showed that when parents were diagnosed, there was a shock. In addition, many parents had feelings of guilt and fear, were concerned and experienced sadness to a greater or lesser extent. Four parents felt inner rejection, three of whom considered aborting the pregnancy. Three other parents were afraid that their child would suffer from the anomaly. Davalbhakta & Hall (2000) came up with similar findings as described above. Their study group consisted of 90 parents (25 prenatal diagnosed, 65 postnatal). In their research, three parents indicated that they had aborted their pregnancy prematurely. Two parents had multiple birth defects in their child. A set of parents had had the pregnancy aborted only due to the CLA/P. Two parents indicated that they had thought about aborting pregnancy but that after counseling they decided against it.
In the Berk et al. study (1999), 38% of 97 parents indicated that the prenatal diagnosis led to anxiety and that parents were in great need of adequate information. A study by Beaumont (2006) describes this fear empirically.

Search and select

The search report refers to the search strategy.
Scientific research on how parents react when a CLA/P is diagnosed in prenatal studies is still scarce. With regard to the methodological aspects related to the available literature, the following should be noted:

1. The recruitment of the research group is often not adequately described and therefore it is not clear whether there is a selection bias.
2. The groups studied are often small and in many cases research has been carried out in only one

treatment team. This makes the results of the study less universal.
3. In many cases measuring instruments are used that are not standardized, not validated and not normalized.

The literature about counseling with the detection of prenatal CLA/P comes mainly from the United States and the United Kingdom. Since socio-cultural, religious and social interests play an important role in the way parents are supervised and choices in the prenatal care path, it is questionable whether the results of these studies can be extrapolated to the Dutch situation. There is no Dutch literature on this particular subject.

Thirteen studies were included[1-13] specifically investigating prenatal counseling in CLA/P (see Table 3 under evidence tables). Different methods of qualitative research were used. Eight studies were found that analyzed the opinion of parents (n=6)[4,7,8,11-13] and caregivers (n=1)[9] or both (n=1)[2] by means of questionnaires. There are two studies [1.10] that studied the viewpoints of parents through interviews with small research groups. Three reviews 3,5,6 with sufficient quality were found.

The quality of the studies is not high methodologically. The studies are mostly observational, consisting of small study populations, no comparative groups, and the selection was often not described. The collection of the data is not described or provided in detail. One method is widely used for qualitative research (no data triangulation). The reviews included are descriptive and not systematically built. As a result, the credibility of the totality of the studies for this particular baseline question is questionable.

Reporting

Last reviewed: 12-01-2011 Last authorized: 12-01-2011

For full reports, evidence tables and any related products, please refer to the Guideline database https://richtlijnendatabase.nl/richtlijn/behandeling_van_patienten_met_een_schisis/startpagina_schisis.html..

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Value of prenatal counseling by a CLA/P team for parents expecting a child with a CLA/P

Primary question

What is the value of prenatal counseling by a CLA/P team for parents who expect a child with a CLA/P?

Recommendation

Prenatal diagnosis should be seen as a process in which the provision of (medical) information and professional psychosocial care plays an important role. Prenatal counseling should aim to provide parents with unambiguous information about what is possible for their child so that he/she can grow up as normally as possible. In order to achieve this goal, it is recommended that the counseling is performed by 2 persons, namely a medical professional and a psychosocial professional.

Psychosocial counseling of parents, who expect a child with a CLA/P, should be an integral part of the guidance of parents by the CLA/P team. In any case, the following issues should be addressed:

- Disappointment; Possible
- guilt;
- Impact on the family;
- How to deal with reactions from the environment;
- intellectual development of the child; psychosocial
- development (resilience e.g.);
- Whether or not it is possible to breast-feed (guilt);
- Possibility to give birth at home;
- Offer contact with other parents in the same position.

It is preferable that the verbal information given should be accompanied by written information.

Every CLA/P team should have a psychologist or social worker, who is adequately trained in acceptance problems, grief processing and system problems in combination with CLA/P, who is available/reachable at least five days a week during business hours for this purpose.

It is recommended that parents be offered follow-up calls where, if desired, acceptance issues (including in the family context) and attention to grief processing can be addressed.

Considerations

Based on the literature studies, it can be concluded that counseling after prenatal diagnosis of CLA/P by specialist responders is highly desirable. Parents need both information and

support in processing the CLA/P diagnosis. Although the literature does not clearly indicate which discipline must provide this counseling, it is obvious that psychosocial aspects of the treatment and support of parents in acceptance and (grief) processing are provided by a trained psychologist or social worker of the CLA/P team.
Two team members must preferably provide the counseling, where on the one hand there should be direct knowledge of the (surgical) treatment, and on the other hand, sufficient knowledge of the psychosocial aspects of having a child with a CLA/P should also be available (Also refer to the “Requirements of the CLA/P team” module”). This is all the more true if there are considerations relating to pregnancy termination. Counseling by two members also reduces the risk of bias in the provision of information. There should always be an opportunity to meet the other members of the team. Each imaging team is expected to anonymously record the ultrasound findings in the NVSCA register Prenatal Diagnostics (see 'NVSCA register' module and last recommendation in that module).
The opinions of the parents from the focus groups support these findings (see relatives). Due to barriers in the financial system, inter alia, distribution problems in the hospital, psychosocial care is not sufficiently guaranteed in the Dutch situation for all CLA/P teams.

Substantiation Conclusions

Level 2	Prenatal counseling of congenital anomalies significantly reduces parental anxiety. *B: Kemp et al. (1998)*

Level 3	The majority (85%-100%) of parents believe that a prenatal diagnosis of schisis followed by counseling makes psychological processing easier. *C: Davalbhakta & Hall (2000), Nusbaum (2008), Rey-Bellet & Hohlfield (2004), Berk (1999), Matthews et al. (1998)*

Level 3	Knowledge and experience of the process parents are going through leads to better care. *C: Nusbaum (2008)*

Level 3	The majority (85-96%) of caregivers think that counseling is useful to parents. *C: Berk et al. (1999), Matthews (2002)*

Summary of literature

Matthews et al. (1998) reported about parents' experiences with prenatal diagnosis. In the period 1990 -1994 13 out of 80 newborn infants with CLA/P (12%) were prenatally diagnosed and counseled by

a CLA/P team; nine parents completed the questionnaire. All the parents liked that they could already have a conversation with the CLA/P team. Prenatal diagnosis made it easier for them to adapt to the new situation. Two-thirds of the group could not mention disadvantages of prenatal diagnosis while one-third of the group felt it made them more anxious. None of the nine parents considered abortion.
In the study of Davalbhakta & Hall (2000), 89% of parents (n=27) liked to know the diagnosis of CLA/P already during pregnancy, 11% would have preferred not to know. 85% felt that this made them well prepared for birth.
For the Rey-Bellet & Hohlfeld study (2004), 29 couples completed a questionnaire. The parents used different sources of information: The midwife, the CLA/P team, the parent support group and the internet. 95% of parents were satisfied with the way they were informed in the hospital. In total, 93% of parents felt that they were well prepared for childbirth. Parents also indicated in the questionnaire that generally people have little knowledge about CLA/P. The knowledge one does have is often biased by negative feelings: The memory of the classmate with the scar, the poor speech and the withdrawn behavior. In the publication of Rey- Bellet & Hohlfeld (2004), 28 out of 29 parents indicated that the prenatal diagnosis and counseling gave them enough time to process feelings and accept the child at birth. In addition, this gave them the opportunity to inform family (especially grandparents and siblings) and friends in good time.
In the study of Nusbaum et al. (2008) in-depth interviews compared experiences of parents who had had prenatal diagnosis and counseling (n=12) with those who only found out postnatally (n=8). The authors themselves cite as benefits of prenatal diagnosis the possibility of psychological preparation (including parental education), better anticipation of neonatal care (for example, nutrition) and the possibility of detecting additional congenital abnormalities (with the option of abortion). As disadvantages of prenatal diagnosis, authors mention emotional problems during the pregnancy, the fact that the abnormality could not be corrected before birth and cost of prenatal diagnosis and counseling.
The parents in the prenatal-diagnosed group mentioned the fact that they had contact with a CLA/P team before birth and had the opportunity to prepare for birth (coping) as a benefit so that they did not have the get used to it after birth. In addition, they indicated that the environment could be informed and it was possible to make contact with other parents who were in the same situation. Some parents in the group who only received the diagnosis at birth would have preferred to know this before, while others were glad they didn't know.
Recent research by Van EK (2009), using a number of questions from the questionnaire of Nusbaum et al. (2008), as well as the opinions of the parents from the focus groups support these findings (see related).
An additional search for the reduction of anxiety during pregnancy resulted in one valid study. In the study of Kemp et al. (1998) parental anxiety was investigated where a prenatal abnormality was seen on the ultrasound. A validated questionnaire was used to measure anxiety before and after counseling. There was a significant reduction in anxiety (from 49.5 to 37 on a scale of 20-80, $p = 0.06$) among parents compared to a control group consisting of parents expecting a healthy child. There was no significant relationship between anxiety and social class or age.
There are two studies that use questionnaires to analyze the opinion of caregivers about prenatal

counseling in the case of a CLA/P. In the studies of Matthews (2002) and Berk et al. (1999) a majority of caregivers (Matthews: Plastic surgeons; Berk: Multiple disciplines) (resp. 106/110 (96%) and 417/570 (73%)) acknowledged parents' need for prenatal diagnosis and counseling. In the study of Matthews et al. caregivers indicated that counseling can be useful to parents.

Search and select

The search report refers to the search strategy.
Scientific research on how parents react when a CLA/P is diagnosed in prenatal studies is still scarce. With regard to the methodological aspects related to the available literature, the following should be noted:

1. The recruitment of the research group is often not adequately described and therefore it is not clear whether there is a selection bias.
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Psychosocial topics to be addressed in prenatal counseling after diagnosis of CLA/P

Primary question

What psychosocial topics should be addressed in prenatal counseling?

Recommendation

Prenatal diagnosis should be seen as a process in which the provision of (medical) information and professional psychosocial care plays an important role. Prenatal counseling should aim to provide parents with unambiguous information about what is possible for their child so that he/she can grow up as normally as possible. In order to achieve this goal, it is recommended that the counseling is performed by 2 persons, namely a medical professional and a psychosocial professional.

Psychosocial counseling of parents, who expect a child with a CLA/P, should be an integral part of the guidance of parents by the CLA/P team. In any case, the following issues should be addressed:

- Disappointment; possible
- guilt; Impact on the
- family;
- How to deal with reactions from the environment;
- intellectual development of the child; psychosocial
- development (resilience e.g.);
- Whether or not it is possible to breast-feed (guilt); possibility to
- give birth at home;
- Offer contact with other parents in the same position.

It is preferable that the verbal information given should be accompanied by written information.

Every CLA/P team should have a psychologist or social worker, who is adequately trained in acceptance problems, grief processing and system problems in combination with CLA/P, who is available/reachable at least five days a week during business hours for this purpose.

It is recommended that parents be offered follow-up calls where, if desired, acceptance issues (including in the family context) and attention to grief processing can be addressed.

Considerations

Based on the literature studies, it can be concluded that counseling after prenatal diagnosis of CLA/P by specialist responders is highly desirable. Parents need both information and support in the processing of the diagnosis of CLA/P. Although the literature does not clearly indicate

which discipline must provide this counseling, it is obvious that psychosocial aspects of the treatment and support of parents in acceptance and (grief) processing are provided by a trained psychologist or social worker of the CLA/P team. Two team members must preferably provide the counseling, where on the one hand there should be direct knowledge of the (surgical) treatment, and on the other hand, sufficient knowledge of the psychosocial aspects of having a child with a CLA/P should also be available (Also refer to the “Requirements of the CLA/P team” module”). This is all the more true if there are considerations relating to pregnancy termination. Counseling by two members also reduces the risk of bias in the provision of information. There should always be an opportunity to meet the other members of the team. Each imaging team is expected to anonymously record the ultrasound findings in the NVSCA register Prenatal Diagnostics (see 'NVSCA register' module and last recommendation in that module).
The opinions of the parents from the focus groups support these findings (see relatives). Due to barriers in the financial system, inter alia, distribution problems in the hospital, psychosocial care is not sufficiently guaranteed in the Dutch situation for all CLA/P teams.

Substantiation Conclusions

Level 3	Naming feelings of disappointment, guilt, reactions from family, friends and surroundings is an essential part of psychosocial counseling after diagnosis of schisis. *C: Young et al. (2001)* *D: Heineman de Boer & Swanenburg de Veye (2010)*

Level 3	The combination of providing information and professional psychosocial care determines how parents deal with the abnormality (learning). *C: Strauss (2002), Jones (2002)*

Level 3	About half of parents need contact with other parents who are in the same situation. *C: Jones (2002), Van Ek (2009)*

Level 3	After diagnosis, psychosocial care with the possibility of follow-up contact should be offered to parents. *C: Rey-Bellet & Hohlfeld (2004)*

Level 4	Verbal information to parents must be accompanied by written information.

Level 2	Children with only a schisis have an average to high-average intelligence as a group. *B: Heineman-de Boer (1985), Swanenburg de Veye (1999)*

Level 2	Children with schisis and associated birth defects have a lower level of development as a group than children with a schisis alone but not lower than average. *B: Heineman-de Boer (1985), Swanenburg de Veye (1999)*

Level 3	Children with and without schisis generally do not differ in terms of social-emotional health. *B: Hoek et al. (2009)*

Level 2	Despite all the barriers that a child with a schisis faces, overall the adaptation and functioning of children with schisis is quite good. *B: Hunt et al. (2005)* *C: Swanenburg de Veye (1999)*

Summary of literature

No specific literature has been found about this, but many things are reflected in the literature mentioned above. As previously described in a previous module, the diagnosis of CLA/P often leads to different emotions and reactions that can overwhelm parents. Feelings of disappointment about the abnormality are often difficult to handle. After all, as parents, you're supposed to be happy with the child you're going to have. You can't turn it down and be mad at your baby because you are feeling so hurt. In addition, the reactions of family, friends and others to the abnormality can be very different and sometimes confusing (Heineman-de Boer & Swanenburg de Veye, 2010).
It is known from literature study that at the time of diagnosis, all parents need clear information. Knowledge makes it possible to prepare you for what is to come.
In a retrospective, descriptive study based on questionnaires (n=40), Young et al. investigated (2001) what information parents needed immediately after birth and what could wait until later. The main topics were nutrition and how to deal with the newborn with CLA/P.
In addition, it seemed important to name the feelings (sadness, guilt, anger, shock). Strauss (2002) believes that the way in which professionals approach the parents can largely determine how parents deal with the congenital abnormality of their ((un)born) child. If professionals 'grieve' with and inform parents about any possible complications, however rare, then it is likely that parents will have an unrealistic picture of reality. Therefore, according to Strauss, professionals should be as neutral as possible in their views. Jones (2002) also believes that the way information is provided influences choices. Information must be realistic and accurate.

Nusbaum et al. (2008) established based on their studies in both groups (prenatal n= 12; postnatal n=8), that parents were not satisfied with the way they were informed. They would have liked to have received written information in addition to verbal information. In addition, there was a need for contact with other parents. The internet was frequently consulted by both groups of parents; a number of parents noted that they were often able to read the most intense stories in the forums they visited. In the Van Ek study (2009), approximately half of the parents in the prenatally and postnatally diagnosed CLA/P groups indicated a need for contact with other parents who were in the same position as them. It emerged from the focus groups that contact with other parents who were in the same position as them was particularly pleasant for practical questions and useful tips, for example in the area of nutrition.
Rey-Bellet and Hohlfeld (b. 2004) argue for psychosocial care after diagnosis, where follow-up contacts with the psychosocial professional are possible.
Children with an isolated CLA/P as a group have an average to high average general intelligence and a slight backlog in verbal development (Heineman-de Boer, 1985, Swanenburg de Veye, 1999). Children with CLA/P and associated birth defects have a lower level of development as a group than children with a CLA/P alone but not lower than average. (Heineman- De Boer, 1985, Swanenburg de Veye, 1999). The variation within this latter group is large, therefore it is important to follow the development of children with CLA/P with associated abnormalities.

During the first 18 years of their life, children with CLA/P undergo multiple corrective operations and are often treated intensively orthodontic and logopedic. The literature does not give a clear picture of what this means for the social-emotional development of these children.
Swanenburg de Veye (1999) concludes that a 'specific CLA/P' personality is not found in the literature. Despite all the barriers that a child with CLA/P sometimes faces during childhood and adolescence, they are normally able to cope with the demands placed on relationships with peers, parents and others.
In a systematic review of the literature on the psychosocial effects of CLA/P, Hunt et al concludes (2005) that research in this area is hardly uniform and consistent. Although problems are reported, the overall adaptation and functioning of children with CLA/P is quite good. Recent survey of Hoek et al. (2009) draws a positive picture of children with CLA/P, who do not differ from peers in terms of their social-emotional health. The children themselves were as satisfied with their appearance as peers without a CLA/P. They also did not have lower self-esteem.

Search and select

The search report refers to the search strategy.
Scientific research on how parents react when a CLA/P is diagnosed in prenatal studies is still scarce. With regard to the methodological aspects related to the available literature, the following should be noted:

1. The recruitment of the research group is often not adequately described and therefore it is not clear whether there is a selection bias.
2. The groups studied are often small and in many cases research has been carried out in only one treatment team. This makes the results of the study less universal.
3. In many cases measuring instruments are used that are not standardized, not validated and not normalized.

The literature about counseling with the detection of prenatal CLA/P comes mainly from the United States and the United Kingdom. Since socio-cultural, religious and social interests play an important role in the way parents are supervised and choices in the prenatal care path, it is questionable whether the results of these studies can be extrapolated to the Dutch situation. There is no Dutch literature on this particular subject.

Thirteen studies were included[1-13] specifically investigating prenatal counseling in CLA/P (see Table 3 under evidence tables). Different methods of qualitative research were used. Eight studies were found that analyzed the opinion of parents (n=6)[4,7,8,11-13] and caregivers (n=1)[9] or both (n=1)[2] by means of questionnaires. There are two studies [1.10] that studied the viewpoints of parents through interviews with small research groups. Three reviews 3,5,6 with sufficient quality were found.

The quality of the studies is not high methodologically. The studies are mostly observational, consisting of small study populations, no comparative groups, and the selection was often not described. The collection of the data is not described or provided in detail. One method is widely used for qualitative research (no data triangulation). The reviews included are descriptive and not systematically built. As a result, the credibility of the totality of the studies for this particular baseline question is questionable.

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Skills required by the person performing the psychosocial counseling with a CLA/P diagnosis

Primary question

What skills should the person performing the psychosocial counseling have?

Recommendation

Prenatal diagnosis should be seen as a process in which the provision of (medical) information and professional psychosocial care plays an important role. Prenatal counseling should aim to provide parents with unambiguous information about what is possible for their child so that he/she can grow up as normally as possible. In order to achieve this goal, it is recommended that the counseling is performed by 2 persons, namely a medical professional and a psychosocial professional.

Psychosocial counseling of parents, who expect a child with a CLA/P, should be an integral part of the guidance of parents by the CLA/P team. In any case, the following issues should be addressed:

- Disappointment; Possible
- guilt;
- Impact on the family;
- How to deal with reactions from the environment;
- Intellectual development of the child; Psychosocial
- development (resilience e.g.);
- Whether or not it is possible to breast-feed (guilt);
- Possibility to give birth at home;
- Offer contact with other parents in the same position.

It is preferable that the verbal information given should be accompanied by written information.

Every CLA/P team should have a psychologist or social worker, who is adequately trained in acceptance problems, grief processing and system problems in combination with CLA/P, who is available/reachable at least five days a week during business hours for this purpose.

It is recommended that parents be offered follow-up calls where, if desired, acceptance issues (including in the family context) and attention to grief processing can be addressed.

Considerations

Based on the literature studies, it can be concluded that counseling after prenatal diagnosis of CLA/P by specialist responders is highly desirable. Parents need both information and support in the processing of the diagnosis of CLA/P. Although the literature does not clearly indicate

which discipline must provide this counseling, it is obvious that psychosocial aspects of the treatment and support of parents in acceptance and (grief) processing are provided by a trained psychologist or social worker of the CLA/P team. Two team members must preferably provide the counseling, where on the one hand there should be direct knowledge of the (surgical) treatment, and on the other hand, sufficient knowledge of the psychosocial aspects of having a child with a CLA/P should also be available (Also refer to the “Requirements of the CLA/P team” module”). This is all the more true if there are considerations relating to pregnancy termination. Counseling by two members also reduces the risk of bias in the provision of information. There should always be an opportunity to meet the other members of the team. Each imaging team is expected to anonymously record the ultrasound findings in the NVSCA register Prenatal Diagnostics (see 'NVSCA register' module and last recommendation in that module).
The opinions of the parents from the focus groups support these findings (see relatives). Due to barriers in the financial system, inter alia, distribution problems in the hospital, psychosocial care is not sufficiently guaranteed in the Dutch situation for all CLA/P teams.

Substantiation Conclusions

Level 4	The psychosocial aspects of the treatment of a child with a schisis and the support of the parents in the (grieving) processing of a schisis determined via SEO in the still unborn child should be offered by a trained psychologist or social worker of the schisis team.

Summary of literature

Although no specific data were found in the literature, it can be concluded from literature studies that counseling after prenatal diagnosis of CLA/P by specialized caregivers is highly desirable. Parents need both information and support in processing the fact that their child will be born with a CLA/P. Although the literature does not clearly indicate which discipline must provide this counseling, it is obvious that psychosocial aspects of the treatment and support of parents in acceptance and (grief) processing are provided by a trained psycho-social professional of the CLA/P team.
The importance of a psychosocially trained professional of the CLA/P team was also emphasized in the focus groups. Emotional guidance with attention to themes such as the impact of diagnosis, annoying reactions of acquaintances, influence on family life and burden of the operations is felt to be very necessary.

Search and select

The search report refers to the search strategy.
Scientific research on how parents react when a CLA/P is diagnosed in prenatal studies is still scarce. With regard to the methodological aspects related to the available literature, the following should be noted:

1. The recruitment of the research group is often not adequately described and therefore it is not clear whether there is a selection bias.
2. The groups studied are often small and in many cases research has been carried out in only one treatment team. This makes the results of the study less universal.
3. In many cases measuring instruments are used that are not standardized, not validated and not normalized.

The literature about counseling with the detection of prenatal CLA/P comes mainly from the United States and the United Kingdom. Since socio-cultural, religious and social interests play an important role in the way parents are supervised and choices in the prenatal care path, it is questionable whether the results of these studies can be extrapolated to the Dutch situation. There is no Dutch literature on this particular subject.

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Medical part of counseling in prenatal CLA/P

Primary question

1. What medical topics should be covered during prenatal counseling to parents who expect a child with a CLA/P (according to parents and professionals)?
2. What caregiver tools are useful to parents in the prenatal counseling process of parents who expect a child with a CLA/P?

Recommendation

Offer prenatal counseling to parents who are pregnant with a child with a CLA/P and have medical information about the CLA/P and its treatment given by one or more practitioners (including a surgeon and someone with psychosocial expertise, such as behavioral or social worker), who is a member of a CLA/P team and who has an understanding of the problems and demonstrable experience in the treatment of children with a CLA/P.

Inform parents about medical topics related to the child with CLA/P in the prenatal counseling such as:

- What is a CLA/P.
- How often does it occur.
- Origin.
- Forms of CLA/P.
- Characteristics.
- Additional anomalies and genetic disorders (discuss clinical genetics referral if necessary).
- Functional consequences.
- Treatment by a team of different specialists. Place of delivery.
- (Breast) feeding and care. Treatment.
- Treatment protocol.
- Surgeries.
- Pain and discomfort for the child.
- Checks with the CLA/P team. Hearing.
- Speech.
- Teeth and jaws.
- Treatment Timeline.
- End result (also limitations such as scars).

Ensure that the caregiver supports the verbal information with written and digital information material, including:

- Information booklet of the CLA/P team.
- Pre- and post-operative imagery.
- Other imagery that supports the oral information, for example in the form of a PowerPoint presentation.
- Feeding aids such as feeding bottle types and teat.

Point out websites that provide objective information to parents.

Considerations

Advantages and disadvantages of counselling

Unfortunately no studies were found in this search which evaluated the effectivity of counselling. It was therefore impossible to answer the PICO question. Nevertheless, a few studies were found that provided useful information about the medical and psychological themes and tools that should be mentioned during the counselling of parents expecting a child with (Greives, 2017; Stocka, 2019; Stockb, 2019).

1. What medical information should be addressed during prenatal counselling to parents who are expecting a child with a cleft lip, alveolus and/or palate (according to parents and professionals)?

Several studies were found in which parents gave their opinion on the topics to be addressed during counselling for prenatal diagnosed clefts of the lip and/or palate. The study of Berk (1999) showed that 87% (84/97) of the parents indicated a need for medical information about the disorder and its treatment. Other topics that parents need in counselling are etiology, chance of additional anomalies, expected medical problems after birth, such as feeding, and treatment (Maes, 1998; Hager, 2002; Jones, 2002; Nusbaum, 2008; Matthews, 1998). The online survey study of Greives, 2017 asked parents (n=112) about the topics that are the most helpful to be discussed during the prenatal visit. The top five consisted of 1. surgical treatments; 2. new-born feeding techniques; 3. team care; 4. genetics; and 5. speech/hearing. Jones (2002) states that, in addition to providing a general overview of treatment, counselling should mainly focus on issues that play a role in the first year of life such as feeding, surgical interventions, ear problems and pain.

The Royal College of Obstetricians and Gynaecologists (RCOG) guideline about prenatal information state that all practitioners performing fetal anomaly screening should be trained to impart information, and that they or another health professional should be available to provide immediate support to parents (RCOG, 2010). Further, that all staff involved should adopt a non-directive, non-judgmental approach, and should not assume, even in the presence of a potentially fatal condition, that the parents will choose to terminate (RCOG, 2010).

Prospective parents could therefore benefit from a comprehensive description of the etiology, likely treatment pathway and prognosis, without health professionals introducing their own values and judgments and/or exceeding their own professional capacity. A referral to cleft specialist should be made soon after prenatal diagnosis, and prospective parents should be directed to a reliable parents/patient organization as soon as possible; CLA/P Nederland (https://CLA/Pnederland.nl) In the Netherlands.

Referrals to cleft specialists would provide prospective parents with further information, emotional support,

And realistic personal accounts of what life is like with a child who was born with , so that they can decide whether further testing and/or termination of pregnancy (TOP) is something they want to pursue. Supplementary written information and trusted website addresses (see below) could also be provided, particularly given that prospective parents may be emotionally distressed and less able to process complex information in the moment.

Trusted websites (May 2021):
Parent/patient organization: www.CLA/Pnederland.nl
Information about cleft lip, alveolus and/or palate and the Dutch cleft teams: https://www.CLA/P.nl/nvsca2/ Thuisarts – patient information: https://www.CLA/P.nl/nvsca2/ www.thuisarts.nl
Information about genetic testing: http://www.erfelijkheid.nl

Stock (2019a) Analyzed data from 217 parents of children born with cleft lip (with or without cleft palate) using a mixed-methods online survey. If a cleft lip, alveolus and/or palate is detected, the way the diagnosis is communicated can considerably influence prospective parents' decision making regarding further testing and TOP. Due to unsatisfactory information and a perceived lack of empathy from health professionals, respondents reported feeling upset, offended and/or anxious following the diagnosis. Some respondents had felt under pressure to decide quickly, with a minority having regretted undergoing amniocentesis, and/or experiencing significant distress at having come close to TOP unnecessarily. Unfortunately, the legal limit of a certain gestational age to terminate a pregnancy, might feel parents under pressure to make decisions quickly (stock, 2019a).

We need to consider that the above-mentioned survey was only shared with parents who are part of CLAPA's community (Cleft Lip and Palate Association UK). While CLAPA's community is significant, it cannot be assumed that this group, nor the subgroup who responded to the survey, are representative of the population in the Netherlands or as a whole. Since all participants were parents of children with , none of the survey respondents had opted for TOP. It is therefore not possible to gain an understanding of the experiences of those who opted to end their pregnancy on the basis of a (with or without associated conditions).

The quality of the information received at the time of diagnosis can considerably influence parents' long-term well-being, as well as their attitudes toward the diagnosis, further antenatal testing, and even TOP (Stock, 2019a).

Stock (2019a) demonstrated their findings emphasize the importance of providing accurate and individualized information to prospective parents, in a sensitive manner, so they can adjust to their child's diagnosis, consider further genetic testing and TOP or prepare for the birth appropriately (Stock, 2019a). Given that antenatal screening for cleft lip is becoming more fully integrated into routine practice in the Netherlands more training for health-care professionals, improved access to reliable information in a variety of formats, and stronger links between local midwifes doing the primary 20-week structural anomaly scan (SEO) and specialist from cleft team may be needed (stock, 2019a based on the British situation).

2. What resources from caregivers are useful in the process of prenatal

counselling for parents expecting a child with cleft lip, alveolus and/or palate (resources such as information leaflets and images, but also practical tools like teats and other aids)?
Four studies were found that provided information on the use of AIDS in counseling parents expecting a child with . In the study of Rey-Bellet (2004) 93% (27/29) of parents were happy to see pictures of children with clefts before and after surgery. Pictures were also an aid to help family and friends prepare for the arrival of a child with . In the study of Matthews (1998) 1/9 parents considered the pre- and postoperative pictures of a child with clefts to be too severe.

The following medical topics related to the child with should be discussed with the parents in prenatal counseling:

- What is a cleft lip, alveolus and/or palate. How
- often does it occur.
- How does it develop.
- Types of cleft lip, alveolus and/or palate.
- Characteristics.
- Additional anomalies.
- Functional consequences.
- Treatment by a team of different specialists.
- Nutrition and care.
- Treatment and treatment protocol.
- Operations /surgery.
- Pain and discomfort for the child. Out-
- patient visits to the cleft team. Possible
- hearing problems.
- Possible speech problems.
- Teeth and jaw outgrouth problems.
- Timeline of treatment.
- End result of treatment (including limitations such as scars).

Parents' opinions about the internet as a source of information vary. Rey-Bellet (2004) found that 17% (5/29) of parents thought it was a good way to find information. However, the pictures published on the internet are perceived by some as scary and because people search at home, this source does not offer the possibility of direct feedback from a healthcare provider (Jones, 2002; Nusbaum, 2008). It is also customary to provide written information.

Values and preferences of patients' parents
It is clear that parents have a great need for information. The literature does not indicate what the professional background of the care provider who provides the information should be. It seems justified from studies from Rey-Bellet (2004) that persons experienced in surgical aspects are important, however the healthcare provider(s) in question should have knowledge and expertise in the whole field of treatment of S. The topics that should be addressed in prenatal counseling previously summarized do not seem to differ from those are routinely used by the majority of (unprepared) parents in the immediate postnatal

phase. The recommendations regarding the topics are based on this experience. It seemed that parents were more interested in short-term issues for their child rather than long-term goals for overall cleft care (Rey- Bellet, 2004).

Costs (resources required)

The ultrasound (including a consultation with a gynecologist) is reimbursed under the basic insurance. Prenatal counseling is however not covered under the basic insurance in the Dutch Health Care system and there may be additional - non-reimbursable - costs for parents due to prenatal consultation with a cleft team. We feel this should not be a reason not to refer patients to a cleft team, however, for some patients this could be a consideration not to start counseling until after birth (in the Netherlands).

Acceptability, feasibility and implementation

Clinical experience has shown that both parents and caregivers seem satisfied with prenatal counseling. It gives parents the space to make choices based on good information. There are no practical restrictions in planning an antenatal consultation with a cleft team. This is available in all locations in the Netherlands.
Prenatal counseling by the cleft team has already been implemented in all academic centers.

Rational

The working group would like to emphasize the importance of providing accurate and individualized information to prospective parents. This should be done in a sensitive manner, so the parents can adjust to their child's diagnosis, and consider further genetic testing and TOP or prepare for the birth appropriately. It is considered important that every parent should speak to a delegation from a cleft team before a possible TOP will take place. Given that antenatal screening for cleft lip is becoming more fully integrated into routine practice in the Netherlands, access to reliable and accurate information in a variety of formats, should be freely available. The working group recommends that prenatal counseling for clefts of the lip and/or palate should always be performed by one or two representatives of a cleft team, preferably including a surgeon and a psychologist or social worker. A close work relation with the obstetric caretaker is an important factor, so that the counselling can be individualized and based on the ultrasound findings. From September 2021 pregnant woman in the Netherlands are offered a 13-week scan as part of research. Woman can only opt to have the 13-week scan if they participate in the scientific IMITAS study. This study is investigating the advantages and disadvantages of the 13-week scan. Possible influence of this opportunity of this scan on the prenatal counseling is not included in the considerations and recommendations yet.

Finally, it might be considered to provide parents with an unborn child with a cleft on ultrasound with the opportunity to speak to other parents that have a child with . In this way parents could get firsthand information, but it may also introduce possible bias. It is possible that the patients' parents' organizations could play an important role in providing peer support. Parks who are willing to act as peer support should receive special training for this purpose.

Background of the Substantiation

Since the introduction of the structural anomaly scan (SAS second trimester) as a routine screening tool for

all pregnant women in the Netherlands in 2007 and the ongoing technological improvement of the ultrasound machines, the prenatal detection of cleft lip, alveolus and/or palate () has increased over the years (Ensing, 2014). From September 2021 pregnant woman in the Netherlands have the opportunity to do a 13- week scan (in a research setting) in addition to the 20-week scan. Prenatal detection allows parents to receive detailed information about the short- and long-term implications of the diagnosis before birth. The goal of the prenatal counselling is to give parents accurate, uniform, and unambiguous information about the possible consequences of the diagnosis of a cleft of the lip and/or palate and future opportunities for their child and to prepare them for birth and the time until the first visit to a cleft clinic. The counselling should include medical as well as psychological information, and tools to prepare parents and their families for the birth of a child with . If diagnosed before 24 weeks of gestation, termination of pregnancy (TOP) is an option that should be mentioned in the Netherlands and should be discussed in more detail in case parents wish to do so. Questions regarding a possible underlying genetic cause and prenatal genetic diagnostic testing are usually directed to a medical geneticist in the Dutch health care system (referral by the obstetrician) and can be of influence for possible TOP.
In the Netherlands, the care for patients diagnosed with S is concentrated in multidisciplinary cleft teams. There is however variation in both prenatal counselling and postnatal care between individual teams.

Search and select

A systematic review of the literature was performed to answer the following question:
What is the effect of prenatal medical counselling on parents of patients with cleft lip, alveolus and/or palate?

P: parents of patients with cleft lip, alveolus and/or palate;
I: Prenatal medical counselling;
C: No counselling;
O: satisfaction, anxiety/concerns, informed choice, termination of pregnancy.

Relevant outcome measures
The working group considered satisfaction as a critical outcome measure for decision making; and anxiety, informed choice, termination of pregnancy as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined the criteria for minimal clinical (patient) important difference for the dichotomous outcome measures; RR < 0.80 of > 1.25) or Standardized mean difference (SMD=0.2 (small); SMD=0.5 (moderate); SMD=0.8 (large).

Search and select (Methods)
The Databases Medline (via OVID), Embase (via Embase.com), and PsychInfo were searched with relevant search terms until 14th of April 2020. The detailed search strategy is depicted under the Tab Methods. The systematic literature search resulted in 317 hits (16 SR, 21 RCTs, 113 observational studies, and 167 others). Studies were selected based on the following criteria: Systematic reviews, RCTs and other comparative studies focusing on medical and/or psychological counselling for parents of patients with . A total or 16 studies

were initially selected based on title and abstract screening. After reading the full text, all 16 studies were excluded (see the table with reasons for exclusion under the tab Methods), thus no comparative studies were selected for the literature summary.

Results

No comparative studies were found that answered the question: What is the effect of counseling on parents of patients with cleft lip, alveolus and/or palate?

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Abortion of pregnancy after a CLA/P diagnosis

Parents have - after receiving a CLA/P diagnosis after performing an ultrasound - several reasons to worry about the future of their child. The aim of prenatal counseling should therefore be to provide parents with unambiguous information about possible opportunities and consequences for their child. Prenatal counseling should address both psychosocial and medical issues. If the diagnosis is made before the 24th week of pregnancy, there is the possibility for parents - weighing all the information - to opt for abortion. Parents must then consider where the partus will take place.

This module is divided into three parts. The first part describes the prevalence of abortions after a CLA/P diagnosis based on literature data. The second part discusses the legal framework. The third part builds on the legal framework and discusses the attitude counselors should take on in the context of questions concerning the termination of the pregnancy.

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Prevalence of abortion in the diagnosis of CLA/P

Primary question

What is the prevalence of abortion in isolated CLA/P in the Netherlands and a number of other Western countries?

Recommendation

The law does not impose an explicit obligation on the practitioners to mention the possibility of pregnancy termination if a CLA/P is detected in an SEO. However, the law says that 'other methods of research or treatment that are eligible' must be communicated (Article 7:448, paragraph 2, subparagraph c).

Practitioners should take a neutral position on abortion if this is discussed. It is the mother who has to decide independently and based on factual information (WAZ law abortion pregnancy).

Considerations

No considerations have been formulated for this module.

Substantiation Conclusions

Level 3	Hard national data on abortion of pregnancy for isolated schisis are not available. Available figures are mainly based on clinics or regions and especially on interviews with parents. It seems that - except in Israel - abortion of pregnancy for a prenatally established isolated schisis is not common practice. *C: Exalto (2009), Wyszynski (2003), Jones (1999), Maes et al (1998), Brohnstein (1996), Blumenfeld (1999)*

Summary of literature

The search strategy (see search report) found 6 studies describing a percentage of parents who opted for abortion.
In the Dutch population, no reliable national data on abortions in isolated CLA/P are available in 2010. One of the reasons for the lack of good Dutch statistics in this area is the fact that the planned central national register system associated with the 20 weeks ultrasound has still not been fully implemented for technical reasons. Regional sources of information are available from the Rotterdam region (Exalto 2009) for the period 2002-2006, from Utrecht (Maars et al. 2010 submitted) for the period 2005-2007 and Amsterdam (Pajkrt, personal communication, unpublished data) for the period 1997-2009. The figures from Rotterdam show 1 abortion for prenatally

diagnosed isolated CLA/P in a population of 33, 20 of which were diagnosed before the 24th week of pregnancy. The figures from the Utrecht region indicate 3 abortions for diagnosed isolated CLA/P in the period 2005-2007. The population in Utrecht has not been given, because in Utrecht the reference is the total number of abortions in the Utrecht region. In the AMC there were 4 abortions out of 72 prenatally diagnosed isolated CLA/P, with no data about at which gestational age it was diagnosed.
In the study of Wyszynski et al. (2003) 165 parents of a child with an already born child with an isolated CLA/P responded to the question of whether they - if they had known - would have wanted to have an abortion. This study shows that no parent would have done so. Also, the 6 parents whose CLA/P was diagnosed prenatally did not want to abort any of them.

In the study of Maes et al. (study population n = 22) a number of mothers pleaded for prenatal diagnosis in the seventh month of pregnancy; then the choice to terminate the pregnancy was no longer relevant.
The studies by Brohnstein et al. (1996) and Blumenfeld et al. (1999) from Israel have a very high abortion ratio in isolated CLA/P. Despite being told in the counseling that the size of the lip cleft prenatally could not be predicted, CLA/P was considered a severe malformation by the parents in these studies. Caregivers would also all opt for abortion if they were expecting a child with a CLA/P. Jones et al. (1999) in their review, provide a possible explanation for these differences between Israel and the United States. The detection of CLA/P in Israel would occur earlier in pregnancy, the burden of carrying a child with a CLA/P would be perceived as more negative and there would be differences in the way counseling takes place. The other studies in which parents opt for abortion in isolated CLA/P do not show any motives.

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Legal framework in the Netherlands concerning the information provision about the possibility of an abortion in CLA/P

Primary question

Legal framework in the Netherlands concerning information to pregnant women about the possibility of pregnancy termination in CLA/P as abnormality in SEO.

Recommendation

The law does not impose an explicit obligation on the practitioners to mention the possibility of pregnancy termination if a CLA/P is detected during a SEO. However, the law says that 'other methods of research or treatment that are eligible' must be communicated (Article 7:448, paragraph 2, subparagraph c).

Practitioners should take a neutral position on abortion if this is discussed. It is the mother who has to decide independently and based on factual information (WAZ Termination of Pregnancy Act).

Considerations

The Termination of Pregnancy Act always offers the possibility (until the 24th week) to have the pregnancy terminated. Women are generally continuously informed about this.
Specifically in the context of SEO, there are two times when information is provided to pregnant women.

1. General information before SEO is performed;
2. Specific information after SEO is performed and an abnormality (i.e. CLA/P) is found.

For both situations, the law does not impose an explicit obligation to mention the possibility of a pregnancy termination if a CLA/P has been detected during ultrasound examination. However, the law says that 'other methods of research or treatment that are eligible' must be communicated (Article 7:448, paragraph 2, subparagraph c).

In the context of SEO, the pregnant woman is generally informed about the possibility of an abortion after the results of SEO have become known. The pregnant woman knows from this that it is normally 'always' possible to have an abortion[6].
It is questionable whether it is necessary explicitly mention the possibility of an abortion in the second phase too (during the SEO when a CLA/P has been detected).
In such a case the woman must be informed about the fact that the child has a CLA/P. This way, she can be prepared for childbirth. She should also be informed about the treatment options of the CLA/P and the expected results of that treatment. This information will have to be adapted to the specific situation and will therefore depend on the severity of the CLA/P observed. Depending on the actual situation, information about the possibility of abortion can also be provided at this stage.

[6] Of course under the conditions laid down in the Termination of Pregnancy Act.

Substantiation Background

All pregnant women in the Netherlands will be given the opportunity to have an ultrasound run around the twentieth week of pregnancy. This ultrasound will be a Structural Ultrasound (hereafter referred to as the SEO), or also called the 20 weeks ultrasound. This ultrasound looks at the growth and development of the unborn child. The main purpose is to investigate the possible presence of an open back or skull. This ultrasound also looks extensively at the development of the child's organs.
Other physical abnormalities may also be seen. Examples of abnormalities that can be seen during SEO: Open back, open skull, hydrocephalus, heart defects, fracture or hole in the diaphragm, fracture or hole in the abdominal wall, absence or abnormality of the kidneys, absence or abnormality of the bones, abnormalities of arms or legs[1]. During SEO, a CLA/P can also be discovered in the child. When drawing up a guideline about the counseling of prenatally established CLA/P, the question has arisen as to what information should be provided to the pregnant woman if a CLA/P is detected in the child during SEO. In particular, it is questionable whether the possibility of pregnancy termination should be mentioned in such a case.
Although several aspects of medical content and ethics should be taken into account in answering this question, the legal aspects of the obligation to provide information will be addressed in this document.
To this end, the relevant legal arrangements will be discussed first and then the scope of the obligation to provide information will be discussed.

[1] Source: www.rivm.nl

Summary of literature

Relevant legal regulations
Law on population screening
The Population Screening Act (WBO) provides that certain categories of population screening are prohibited if the Minister did not issue a license for such screening (article 3, first paragraph, WBO). The WBO indicates when it concerns a population screening (Article 1(c)). It also indicates the existence of a compulsory population screening (Article 2(1) of the WBO). Based on these provisions, it can be concluded that SEO is covered by the Population Screening Act. However, this law does not impose any particular requirements on the information requirements for SEO.

WGBO
A medical treatment agreement shall be concluded between the person performing the population screening and the participant. The Medical Treatment Agreement Act (WGBO) therefore applies to population screening. This means that the rights recorded in mandatory provisions of Articles 7:446-7:468 BW also apply to participants in a population screening[2].

One of the components of the WGBO is the so-called 'informed consent scheme'. This arrangement is set out in Articles 7:448 and 7:450 of the BW, which sets out the obligation to provide information and the requirement for consent respectively. For the patient, the information he obtains and the consent he must give are an expression of his self-determination. By striving for informed-consent, the responder, for his part, expresses the fact that he gives space and value to the patient's autonomy. Choices are retained for patients who are not able to decide whether or not to participate in the treatment based on sound information.
Taking the patient seriously involves being guided along the road to make a responsible decision and being aware of the consequences of refusal. The caregiver may use his full power of persuasion[3].
The WGBO also includes a right to not know (Article 7:449).
In Article 7:448, the obligation to provide information (where relevant in this context) is set out as follows:

1. The responder shall clearly inform the patient, and on request in writing, about the intended examination and the proposed treatment and about developments in the patient's examination, treatment and state of health. (……)
2. In carrying out the obligation laid down in paragraph 1, the responder shall be guided by what the patient reasonably needs to know with regard to:

a. the nature and purpose of the examination or treatment which he considers necessary and the actions to be carried out;
b. the expected consequences and risks to the patient’s health;
c. other methods of examination or treatment that may be considered;
d. the state and prospects of his health in terms of the research or treatment.

In the context of this memorandum, the question is in particular how this general obligation should/can be implemented in practice.

Obligation to provide information
There are several times when information about SEO can be provided. Depending on whether the information to be provided can be determined at that time.

1. Provide information before SEO is performed;
2. Information after SEO is performed and an abnormality (i.c CLA/P) is found.

The purpose of the information is different from time to time. The information provided at the first moment is intended to make a choice as to whether or not to participate in the SEO. The information provided at the second moment is intended to make a decision about the results of the SEO.
The content of the information therefore also depends on the purpose of the information provision. Generally, the information provided at the first moment will be more general than the information provided at the second moment.

What information do you provide regarding the possibility of abortion?
RIVM, in collaboration with the professional groups involved in obstetrics, has published a brochure in which pregnant women are informed about the possibility of participating in SEO. This brochure explains the main purpose of SEO and the conditions that can be found in SEO. The brochure also explicitly states that 'if serious birth defects are detected, there is a possibility of aborting pregnancy, the results of SEO may at some point lead to an abortion being considered'. In that brochure, the pregnant woman is generally advised that she may consider an abortion based on the results of SEO.
A recommendation from the Health Council also states that the results of SEO can be used to decide to abort the pregnancy. According to the Health Council, the goal of SEO is to discover what is different in order to include a choice possibility. The screening itself aims to inform the prospective parent(s) about the possible presence of the condition in order to provide them with timely options, ranging from the possibility of preparing for the birth of a child with an abnormality to the possibility of deciding to abort the pregnancy[5].
The pregnant woman should also be informed when a CLA/P is detected during SEO. The law also imposes an 'only' obligation to provide information in this situation. However, this information should be tailored to the specific circumstances of the case. This means that the information must be tailored specifically to the outcome of the SEO and to the individual's situation. In addition, the purpose of the information must be taken into account. In my view, the information provided is mainly intended for preparing for the birth of a child with CLA/P and informing the parents about treatment options etc.
For example, the obligation to inform pregnant women about the severity of the disorder (CLA/P), the possible treatment methods (according to the state of the art) and the possible results and consequences of this treatment. The law does not impose any specific obligation to inform about the possibility of an abortion in such a case, but it is conceivable that this should be discussed with the pregnant woman.
The caregiver will have to answer specific questions from the pregnant woman about the possibility of an abortion.

Considerations that could play a role when deciding to specifically inform the parent about the possibility of an abortion may include:

- The severity of the CLA/P.
- The treatment possibilities according to the state of science.
- The expected results of treatment options and the prospects of the child.
- The personal views of the pregnant woman and generally accepted views within the profession.
- The knowledge that women in general know that a pregnancy termination is legally permitted up to a gestational age of 24 weeks.
- The knowledge that the pregnant person has been previously informed in the context of SEO about the possibility of a pregnancy termination via the brochure of RIVM/joint obstetrical active professions.

If, by the way, there is a consensus within the profession about whether or not to actively inform the parents about the possibility of a pregnancy termination, then that is the 'standard'. It should then be followed in principle.

[2] See for example M.C.I.H. Biesaart, 2008, T&C Health Law, Introductory Note, Note 3. Law on population screening.
[3] From: From Law to Practice, Part 2, Information and Consent, page 11, www.knmg.nl/publicatie
[4] See also, for example, the national quality requirement of informed consent and privacy, www.rivm.nl.
[5] Health Council: Population screening law. Initiate a national prenatal screening program. Down syndrome and neural tube defects (297Kb), October 5, 2006, www.rivm.nl.

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Attitudes of the counselor towards parents in the context of questions concerning the termination of pregnancy

Primary question

What is the attitude of the counselor towards parents in the context of questions about aborting pregnancy in case the SEO establishes a CLA/P?

Recommendation

The law does not impose an explicit obligation on the practitioners to mention the possibility of pregnancy termination if a CLA/P is detected during a SEO. However, the law says that ‘other methods of research or treatment that are eligible’ must be communicated (Article 7:448, paragraph 2, subparagraph c).

Practitioners should take a neutral position on abortion if this is discussed. It is the mother who has to decide independently and based on factual information (WAZ Termination of Pregnancy Act).

Considerations

Scientifically reliable data on both incidence and process are not available or hardly available. More research is urgently needed.
The working group agrees that caregivers involved should maintain a neutral attitude towards prenatal CLA/P, but should inform parents as fully as possible.
For the description of the further guidance of parents who choose to have the pregnancy aborted, reference is made to the guideline 'Guidance of women considering abortion' by the Dutch Society of Abortion Physicians and the Dutch Society for Gynecology and Obstetrics.

Substantiation Conclusions

Level 3	Professionals involved in prenatal schisis counseling believe that counselors should adopt a neutral attitude to the issue of pregnancy termination as much as possible. *C: Strauss (2002), Matthews (2002)*

Summary of literature

Two studies have been found (search strategy see search report) in which the attitude of the counselor was analyzed. In the Matthews study (2002), which sent a questionnaire to plastic surgeons, a majority of respondents felt that caregivers should conduct non-directive counseling. With non-directive counseling, the respondents mainly refer to not influencing the parents' opinion about the abortion issue in CLA/P. 8% of respondents

indicates that they do share their negative view of abortion in CLA/P with parents. In this study, 88% of plastic surgeons found it ethically justifiable to provide information about pain that children may experience from reconstructive surgery. The author concludes that surgeons are not accustomed to keeping their opinions to themselves like clinical geneticists. Surgeons would be aware of the fact that the principle of informed consent can be influenced by their method of providing information.
Strauss (2002) stresses that professionals should be neutral when it comes to an opinion about the termination of pregnancy in the case of CLA/P. They must respect the parents' right to decide autonomously. Abortion may be discussed, but only if this question comes from the parents.

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Delivery in case of prenatally established CLA/P

Primary question

In the case of prenatal CLA/P, where is the best place for delivery?

Recommendation

In prenatal isolated CLA/P, there are no medical restrictions on the location of the parturition.

If the CLA/P is part of more extensive congenital problems based on genetic research and/or ultrasound findings, delivery should take place in a tertiary center.

Considerations

When choosing the location of the partus, the safety of mother and child are paramount. In this context, it is important to distinguish between an isolated CLA/P and a CLA/P as part of more extensive congenital defects ('CLA/P plus' with other fetal structural and/or chromosomal aberrations), as far as this can be determined prenatally.
For the prospective mother, the presence of an isolated CLA/P in the child does not, as far as is known, entail an increased risk of obstetric complications around the partus. There is also no known increased risk of perinatal complications in an isolated CLA/P. In this context, the choice and desire of the future parent(s) will be decisive with regard to the location of the partus.
In case of CLA/P plus (other fetal and/or chromosomal aberrations) the risk of perinatal complications may be increased. This may also be the case for the mother in such cases where delivery is indicated in the clinical setting, preferring the (satellite) center where prenatal diagnosis has also been performed and the CLA/P team is present.

Substantiation Summary of

Literature

No literature was found about this particular subject. This can be explained by the Dutch obstetrical organization (1st, 2nd and 3rd line), where the obstetrical estimated low-risk 1st line pregnant women have the option to give birth at home) differs from the surrounding countries.

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Practical matters concerning birth in prenatally established CLA/P

Primary question

- How quickly should the child born with a CLA/P be seen by the CLA/P team?
- Any child with a CLA/P should always be referred to a pediatrician and/or clinical geneticist after birth.
- What is the most optimal nutrition strategy/method of feeding in the case of CLA/P?
- How can we improve the knowledge of CLA/P in the maternity ward and the caregivers in the first line?

Recommendation

Any child born with a CLA/P should preferably be reported to the regional CLA/P team within 24 hours of birth. The CLA/P team must take the necessary measures.

In the event of feeding problems, the CLA/P team's logopedist must be engaged.

A child born with a prenatally established CLA/P and parents who have completed the prenatal counseling course should be seen by the CLA/P team within 2 weeks after it was reported. Before this (if necessary, by telephone), the CLA/P team can assist parents or health professionals in the 1st line with advice.

Any child born with a CLA/P should be examined by a pediatrician and/or clinical geneticist within 2 weeks of birth to identify or rule out any known or unknown additional birth defects.

Parents should be adequately educated prenatally about feeding children with a CLA/P.

CLA/P teams have the responsibility to provide the 1st line and maternity wards with information about feeding a child with a CLA/P and to provide further training if desired.

Considerations

How quickly should the child born be seen by the CLA/P team?
The time between birth of the child and consultation of the CLA/P team is arbitrary and cannot be established from literature data. The nature of the complaints and any additional abnormalities determine how quickly a child should be referred and seen by the team of experts.
Another factor, which determines the speed and necessity of the referral, is the 1st line's existing knowledge about the condition and the expected feeding problems. Experience has shown that many older parents struggle with feeding problems due to lack of knowledge among doctors and health care professionals. A quick reference to a knowledge center can quickly fix this type of problem.

The most important practical aspect in direct postnatal care is good information on feeding methods and how to use resources.
In this context, a distinction can be made between children, who have already been diagnosed with CLA/P prenatally and children, who were unexpectedly born with a CLA/P. In the first case, it can be assumed that prenatal counseling has been carried out adequately and that preparations for the postnatal phase, particularly with regard to feeding, have been made. In these cases, if the child continues to make a healthy impression when examined by the midwife, there seems to be no hurry to consult the CLA/P team. In the case of an unexpected birth of a child with CLA/P, the situation is different. Parents are not prepared and need information in the short term similar to if the child is diagnosed prenatally with a CLA/P (see modules 'Counseling when diagnosed with a CLA/P'). Also, no feeding preparations have been made. Short-term support from the expert team is then indicated.

Should a child with a CLA/P always be examined by a pediatrician and/or clinical geneticist?
From literature it is known that a CLA/P can be part of more extensive congenital defects, see module 'Additional Genetic examination'. It is also known that not all additional abnormalities are visible on the ultrasound and that some abnormalities are only more apparent later.
Based on this, it seems sensible to have every child born with any form of CLA/P examined carefully by a pediatrician.
In addition, it seems wise to consult a geneticist again - if possible, the one who was involved prenatally - in order to avoid any further heredity examination, also depending on the wishes of parents and findings of the pediatrician.

What is the most optimal nutrition strategy / method of feeding in the case of CLA/P?
Children with a cleft lip and cleft lip-jaw may, if desired, be breast-fed or drink from the bottle with a normal teat.
Children with a lip, jaw and or palate cleft are often unable to create strong pressure in the oral cavity. As a result, self-feeding is not successful and the baby will take extra air with the food to the stomach. This will case these children to have more frequent intestinal cramps and they will have a greater tendency to spit.
If the child is unable to suck, it will make it more difficult to drink from the breast or a bottle without extra help. As a result, the length of feeding increases and the child is at risk of insufficient fluid and calorie intake.
Parents' experience shows that the maternity wards and/or caregivers in the first line do not have sufficient experience with feeding problems in newborn babies with CLA/P. For this reason, it has been decided to include the most important opinions on feeding in this directive.
Practical considerations: When bottle feeding, the following practical issues are important: Feeding posture: A half-seated position is the best position to avoid choking and swallowing additional air. This makes use of gravity and allows air to escape more easily from the stomach.
Feeding time: On average, a child’s feeding takes 10 minutes. In a child with CLA/P, the feeding time can sometimes be significantly longer. This will cause the child to become tired and he/she will rest. This also means that there will be little time left for parents to do fun things with their infants. With the Haberman system (also called: Special Need Feeder, see figure) the feeding time

can more or less return to normal. The Haberman system is a teat with a large tank and a unidirectional valve mechanism (once in the teat, the milk cannot flow back into the bottle). This type of bottle allows parents to control the amount of food in the infant's mouth by squeezing the tank portion of the teat. Proper instruction on how to squeeze the tank area is important. To prevent choking and better control, the teat can be placed skew in the mouth so that the milk flow does not directly target the posterior pharynx wall.

In general, feeding problems are at the forefront (see above). Respiratory problems are also to be expected in a cleft palate micrognathia. In addition, CLA/P is sometimes associated with other congenital abnormalities. It goes beyond the scope of this directive to discuss all possible associations. A consultation with a pediatrician or clinical geneticist during one of the first visits to the CLA/P team is required to determine if associated abnormalities are present.

How can we improve the knowledge of CLA/P in the maternity ward and the caregivers in the first line?
The focus groups showed that maternity wards and caregivers in the first line generally do not have sufficient knowledge about CLA/P. They are an important point of contact for parents in the care of their baby with CLA/P. Clear information on abnormality, care and treatment of a baby with CLA/P was recommended by the focus groups.

Knowledge can be distributed via different routes. Leaflets left with midwives, general practitioners and consulting firms. In addition, information will need to be made available via the web to provide professionals and parents with information quickly.

Substantiation

Summary of Literature

No articles were found in the literature, which are directly related to the speed of referral, knowledge in maternity wards about CLA/P and feeding.

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Requirements for feedback of postnatal outcome in prenatally established CLA/P

Primary question

What are the requirements for the feedback of the postnatal outcome to the gynecologist/sonographer/midwife/general practitioner?

Recommendation

After birth, feedback should be given to all perinatological parties (general practitioner, midwife, gynecologist, prenatal diagnostic center, pediatrician).

If the CLA/P is confirmed in the center for Prenatal Diagnosis, the referrer should be informed about the findings and the policy to be pursued as soon as possible. This is to provide the patient with unambiguous information.

Considerations

As it is very important for the patient that all caregivers involved are well informed, proper arrangements should be made for feedback.
The quality assurance/quality control of the Executive Screening center requires optimal follow-up. This can only be done if there is proper postpartum or postnatal feedback of findings at the prenatal diagnostic center.

Substantiation Conclusions

Feedback of findings and policy to be implemented as soon as possible (< 2 working days) by telephone to the midwife (interesting though, midwife has already received feedback from PND).

Written reporting of findings and policies to be followed.

Feedback to GMP/sonographer/midwife/gynecologist (all midwife responders involved) by postnatal expert team immediately after first interview.

Summary of literature

No literature was found on this specific primary question.

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Reducing the risk of CLA/P by taking additional folic acid

Primary question

Does the administration of additional folic acid around conception and in the first embryonic weeks reduce the risk of developing a CLA/P?

Recommendation

In view of the fact that supplementation of folic acid, either in the form of folic acid alone or in the form of multivitamins, prevents neural tube defects and that this may also be the case for the CL/P CLA/P category, the recommendation of the health council should also be endorsed for CLA/P.

Given that neural tube defects, CL/P and CP are mainly fusion defects, it seems plausible on theoretical grounds to prolong the periconceptional folic acid use recommended by the Health Council for 4 weeks.
However, further investigation is necessary to determine whether the recommended period of folic acid use of at least 4 weeks before to 8 weeks after conception should be maintained or that extension to the entire first trimester is required to cover the types of CLA/P (fusion defects) within categories CL/P and CP.

Considerations

One of the questions asked above is whether folic acid has an effect on categories CL/P, CP or both. The data from the NVSCA registration CLA/P show a significant decrease in the prevalence of CLA/P in the Netherlands over the period 1997-2007, based only on a decrease in the prevalence of CL/P with and without additional abnormalities (Rozendaal et al. 2009 and 2010). For the cause of this CL/P decline, two hypotheses are presented by the authors: (I) an increase in the second trimester pregnancy abortions (NB. Only CL/P can be seen prenatally through SEO) and ii) an increase in folic acid use.
The recommendation of the Dutch Health Council for folic acid use is 0.4 mg/day from at least 4 weeks before to 8 weeks after conception. The supplement includes both folic acid and multivitamins with folic acid (Walle, etc.) 2008). The largest number of CL/P occurs in the first 7 weeks after conception; these are the so-called fusion defects, i.e. complete clefts of the lip and (in)complete clefts of the jaw (Luijsterburg etc. 2010). The incomplete clefts of the lip and/or jaw develop during the palate fusion process; the fused defects of the palate occur after 7-8 weeks post-conception. Both the incomplete lip/jaw clefts and the palate clefts thus arise outside the advisory period of folic acid use (for complete and incomplete clefts, see module 'CLA/P: Definition'). The cellular biological mechanism of the fusion defects of the lip/jaw/palate and those of the neural tube defects such as anenceplalie and spina bifida aperta are similar (Moorman et al. 2007). The fusion process from the neural ramparts to the neural tube and thus the neural tube defects all occur within the recommended period of folic acid use, which may explain the prevalence decrease of these defects in timing. The fact folic acid use decreases the prevalence of neural tube defects is accepted worldwide (Wehby and Murray et al. 2010).
Further examination of the types of CLA/P within the categories CL/P and CP in relation to timing and the

dosage of folic acid and multivitamins in combination with maternal characteristics will have to indicate whether the ponated hypothesis II holds firm. Such a study, in which the characteristics of the mother, such as smoking behavior etc., can also be taken into account, can be carried out of the data of Eurocat Noord-Nederland (Walle et al. 2008) are combined with those of the NVSCA. As far as is known, this research design is unique because Eurocat distinguishes between the use of folic acid and multivitamins and the NVSCA is the only register that distinguishes the morphology of the type of CLA/P within the categories.

Substantiation Conclusions

Level 2	The use of multivitamins with or without folic acid around conception and in the first embryonic weeks is likely to decrease the risk of the CL/P schisel category. *B: Johnson and Little et al. (2008), Badovinac et al. (2007)*

Summary of literature

Reliable meta-analyzes on the role of folic acid in the etiology of CLA/P were published in 2006 and 2008 (level of evidence: A1) (Johnson and Little et al. 2008, Badovinac et al. 2007). A review was subsequently published in 2010, which not only describes the results of the main studies of the effect of folic acid and/or multivitamins on CLA/P, but also discusses the limitations of these studies (Wehby and Murray et al. 2010).
Many studies have been conducted on the etiology of cleft lip with or without cleft palate (CL/P) and cleft palate only (CP) and the role of folic acid or folic acid containing multivitamins, suggesting a protective effect on the development of CLA/P. However, since most studies have not been randomized, the effect of folic acid cannot be separated from the action of other components of the multivitamin preparations in the interventions. This makes the interpretation of the results difficult.
First the two meta-analyzes will be discussed, followed by the review. In the meta-analysis of Johnson and Little (Johnson and Little et al. 2008) a broad search was performed and the analysis was not limited by language; the authors included more than 70 studies. Badovinac et al. (Badovinac et al. 2007) Included 17 only English-language studies, distinguishing only prospective studies (intervention trials and cohort studies) and case-control studies. Johnson and Little, however, distinguished several study subgroups, allowing them to investigate the following relationships: The use of supplements (folic acid and/or multivitamins) and the risk of a CLA/P (observational studies and randomized controlled trials (RCTs); the use of supplements and the likelihood of recurrence of CLA/P; folic acid use quantified from diets, whether or not in combination with the use of supplements and the development of CLA/P; the prevalence of CLA/P before and after using folic acid supplements; folate status (folate is the unstable form of folic acid that occurs in the food and is active in the body) and the formation of CLA/P; genes involved in folic acid metabolism or transport and the formation of CLA/P; and gene environment interactions and the development of CLA/P.
The above differences in design of the studies means that the results of the meta-
analysis cannot be easily compared.

Review results from Johnson and Little

NB. In the study of supplements, Johnson and Little grouped the studies that speak of folic acid and multivitamins containing folic acid under folic acid and in multivitamins it is not known whether or not they contain folic acid.

Observational studies

The meta-analysis included 22 studies. Most of these studies included women taking folic acid or multivitamins around conception and subsequent during the first three months of pregnancy. This use was associated with a reduced risk of CL/P (OR 0.75 [95% CI 0.65-0.88]; p<0.01; I^2 56)[7] and, albeit less, at CP (OR 0.88 [95% CI 0.76-1.01]; p=0.13; I^2 26). When the analysis was limited to only those studies specifically mentioning the use of folic acid (n=13), the association became less pronounced for both CL/P (OR 0.82 [95% CI 0.70-0.97]; p=0.02;$^{I\,2}$ 49) and CP (OR 0.95 [95% CI 0.79-1.14]; p=0.13; I^2 32). When the analysis was limited to the use of multivitamins alone (n=18), the results were consistent with those of the use of folic acid or multivitamins for both CLA/P categories.

The following examples show that the timing of the use of supplements also has an effect on the risk of CLA/P. For women taking supplements before conception (9 studies available), the risk of a CLA/P is reduced: CL/P (OR 0.65 [96% CI 0.50-0.86]; P=0.07; I2 45) and CP (OR 0.70 [95% CI 0.51-0.98]; P=0.26; I2 21). It should be noted that the use of supplements at an early stage of conception indicates pregnancy planning and a generally healthier lifestyle, such as no smoking and no alcohol consumption. For women who started taking supplements after the etiologically relevant period, i.e. the third month of pregnancy for CL/P and the fourth for CPO, respectively, no reduced risk of CLA/P was found (2 studies available). There was no publication bias in the study subgroup of observational studies.

RCTs

An RCT was found in which women wishing to become pregnant were randomized to the periconceptional use of folic acid containing multivitamins. However, the primary outcome was non-CLA/P, which meant that the study had insufficient power to demonstrate a significant association.

Repeat chance studies

In these 3 studies, the authors included women who had previously had a child with CLA/P. One of the three also included families in which one or both parents had a CLA/P.

Despite the large variability in the given dose of multivitamins containing folic acid between studies (0.5, 5 and 10 mg/day), similar results were shown. The meta-analysis showed low heterogeneity and a reduced risk of CL/P (relative risk (RR) 0.33 [95% CI 0.15-0.73]). This also indicates that there is probably no dose-response relationship (i.e. same effect despite a large difference in folic acid dose).

Studies on folic acid levels in diet

For studies (n=7) measuring folic acid in the diet of women who received a child with a CLA/P and in the diet of a control group, no meta-analysis was possible due to differences in: (I) the definition of

quantification of folic acid intake between studies; and (ii) inclusion criteria. Although there was a suggestion of an opposite relationship between folic acid and CLA/P, overall results varied and wide confidence intervals were caused by the small study populations.

Studies before and after folic acid supplements
For the meta-analysis, studies were used from Australia (n=2), Canada (n=1) and the USA (n=4). The prevalence of CL/P decreased slightly after the introduction of folic acid supplements (Prevalence Ratio (PR) 0.95 [95% CI 0.91-0.99]; p=0.46; I^2 0). This decrease was not seen for CP (PR 1.01 [95% CI 0.90-1.15]; p<0.01; I^2 75). It is noteworthy that the prevalence of CL/P and CP remained or increased in Australia where folic acid supplements became optional and decreased in the US and Canada where this food supplement became mandatory. This decrease in prevalence may be part of a natural trend or may be caused by a general improvement in lifestyle and environmental factors and should therefore not be directly explained by the increased intake of folic acid. In addition, it was a very small decrease in prevalence, so if folic acid already played a role in the etiology then it is small.

Biochemical markers and folate status
The results between the studies (n=6) comparing biochemical markers of folate status measured as plasma folate and erythrocyte folate were not consistent between case and control mothers. In subjects with low folate status, both an increased and a reduced risk of receiving a child with CLA/P was found. Meta-analysis could not be performed due to differences in definition of subgroups between studies.

Genes involved in folic acid metabolism or transport
None of the analyzes concerning genes involved in folic acid metabolism or transport (n=25) provide convincing evidence that they are relevant to the etiology of CLA/P.

Gene environment interactions
No meta-analysis of gene-environmental interactions was feasible due to the small number of studies (n=6). A total of 10 different associations were described: Combinations of outcome (CL/P, CP), exposure (supplements, folic acid content in diets) and genotype (child, mother); there were differences in definition of reference groups, and most studies had insufficient power to demonstrate an association.
In conclusion, according to Johnson and Little, there is no strong evidence that folic acid alone plays an important role in the etiology of CLA/P. The best evidence that there may be an association between the use of multivitamins (with or without folic acid) and a protective effect on CLA/P was provided by the observational studies. However, it should be noted that a component of the multivitamins other than folic acid may be responsible for the protective effect observed. Which component(s) that could be is difficult to say, because the composition of the multivitamins is usually not given.
NB. Incidentally, the decrease in the prevalence in CLA/P following the mandatory food supplement with folic acid was by no means as marked as the decrease in the prevalence of neural tube defects.

Results from Badovinac et al.

Prospective studies (intervention trials and cohort studies)

In the meta-analysis of Badovinac et al. no distinction was made between folic acid and multivitamins containing folic acid. Therefore, this discussion refers to supplements containing folic acid. The use of folic acid-containing supplements resulted in a reduced risk of CL/P (RR 0.51 [95% CI 0.26-0.98]; Q 3.91 and p=0.27)[8] and no relationship to CP (RR 1.19 [CI 95% 0.43-3.28]; Q
1.99 and p=0.37). This meta-analysis includes 5 studies, including both studies involving women who were expecting their first child (3 studies) and studies involving women who had a previous child with CLA/P (2 studies).

Case control studies

The meta-analysis of 12 studies on the use of folic acid-containing supplements resulted in a reduced risk of CL/P (RR 0.70 [95% CI 0.63-0.78]; Q 30.91 and p=0.001) and a weaker relationship with CP (RR 0.80 [95% CI 0.69-0.93]; Q 7.13 and p=0.624). Following the use of the random effects model for CL/P due to significant heterogeneity, a reduced risk for this category was also found (RR 0.72 [95% CI 0.58-0.87]).

If the studies that did not meet the supplement period of the first trimester were excluded (n=2), the relationship was less pronounced for CL/P (RR 0.73 [95% CI 0.57-0.92]) and for CP (RR 0.81 [95% CI 0.69-0.95]).

For both the prospective studies and the case-control studies, no publication bias was found in this meta-analysis.

In conclusion, with the exception of the prospective studies for CP (n=3), Badovinac et al. demonstrated a consistent protective effect of the use of folic acid-containing supplements during pregnancy. However, it is not certain that the folic acid was responsible for this effect, as the supplements also contain other nutrients. Moreover, it is likely that the lifestyle of women who use supplements is healthier than that of women who do not. The meta-analysis has not been corrected for confounders such as smoking (NB. More women in the CLA/P population were smokers than those in the control group, Badovinac et al. calculated that based on an enrolled
study). Thus, the hypothesis of the protective effect of folic acid-containing supplements on the formation of CLA/P is supported, but is tempered by the amount of potential bias.

Both studies conclude that the use of multivitamins containing folic acid around conception and the first embryonic weeks is protective, although it should not be said that folic acid is specifically responsible for this.

Results from Wehby and Murray

This review describes the findings of the main studies (for the vast majority of observational studies), including the above meta-analyzes, regarding the possible preventive effects of folic acid-containing supplements on CLA/P. The authors agree with the conclusions of the meta-analyzes, although they think that the preventive effect of the addition of folic acid alone is more obvious than that of the other micronutrients that have been studied so far, such as vitamins B1 and B6, myo-inositol and zinc.

They note that the following questions still need to be answered: Whether folic acid does indeed prevent CLA/P and/or reduce the chance of recurrence of CLA/P; whether it reduces the prevalence of CL/P, CP or both; and finally whether low or high doses are effective in prevention. The existing studies could not answer

these questions, because it is subject to data and design restrictions. Examples include the lack of randomization of supplementation, the lack of differentiation between folic acid only and other supplements, the inaccurate description of the dosage and time period of the supplementation, the inclusion of a too small number of individuals, and the lack of data on health status (e.g. epilepsy) and lifestyle (e.g. smoking and alcohol consumption) of women.
Only a randomized, double-blind, placebo-controlled trial with a sufficient number of subjects can demonstrate the effects of folic acid. However, this study design is unethical with regard to the prevention of neural tube defects. An alternative is to select low and high doses of folic acid in a randomized double-blind study. Currently, a clinical trial has been completed in Brazil, where high-risk women were randomized to use folic acid at low (0.4 mg) and high (4.0 mg) concentrations. Unfortunately, the results of this study are not yet available. In addition, the design of future observational studies and of the analytical models should be optimized so that the above questions can be answered.

[7] Abbreviations: OR — Odds Ratio; and 95% CI — 95% Confidence Interval.
In the Johnson and Little study, DEP value is derived from the Cochran's Q test and the 2 I value from the I^2test, both of which test the heterogeneity of the studies being compared. Homogeneity means that all results of the studies included are comparable. If the results of studies vary widely, there may be both clinical and statistical heterogeneity. In clinical heterogeneity, the patients enrolled may vary from study to study (e.g. diagnosis and in-/exclusion criteria) and the treatment (e.g. duration or dose) may differ. Statistical heterogeneity may be related to publication bias, methodological deficiencies and the use of incorrect outcome measures. A value of I^2 <0.25 indicates a low heterogeneity, 0.25-0.50 indicates a moderate heterogeneity and above 0.50 indicates a high heterogeneity.

[8] The Q-value in Badovinac et al. comes from the Q-key, which is used for testing heterogeneity. A Q of 0 means that there is no heterogeneity. For each Q-value a p-value was given for testing the zero hypothesis that the Q = 0 at a = 0.10. If there was significant heterogeneity, the so-called random effects model was used instead of the fixed effects model, where each study counts equally.

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Implementation of guideline for counseling after prenatally established CLA/P

Primary question

Implementation of guideline counseling after prenatally established CLA/P.

Recommendation

In addition to disseminating the Directive to relevant professions and organizations, an implementation plan should be drawn up and implemented. Measuring indicators and feedback based on them, as well as interactive continuous training, should be part of the plan.

Considerations

There is no point in drawing up a directive without ensuring implementation. The professions and organizations involved in prenatal counseling in CLA/P should therefore collaborate and take the initiative to draw up a concrete implementation plan and then implement it. Feedback based on indicators and interactive continuous training should be part of this. In the next paragraph, the commission sets out a first step in drawing up indicators based on the directive. In implementing the Directive, the professional associations could use the quality check by asking them about the use and application of the Directive. It is also important that the Directive is made widely known among the professions and organizations involved in prenatal counseling in CLA/P. This can be done, among other things, by posting on the website of the parties concerned, articles in (trade) magazines and presentations at relevant conferences and regional meetings. The implementation of the Directive could be further strengthened by the preparation and dissemination of a lay/patient version.

Substantiation Conclusions

Level 1	Interactive education (educational outreach), audit & feedback methods, as well as reminders (during consultation) are effective strategies and in most cases also effective in bringing about change. *A1: Jamtvedt (2006), Grimshaw (2004), Prior (2009)*

Summary of literature

Implementation is the process and planned introduction of innovations and/or changes of proven value with the aim of giving them a structural place in the (professional) action, in the functioning of organization(s) or in the structure of the health care system (Grol 1998, Regiraad 2009). The focus on implementation of guidelines is lagging behind the focus on development of guidelines. There is an enormous amount of activity in the field of Directive development and quality, but its practical application is not sufficient.
Several reviews show that the poor implementation of guidelines results in a limited change/improvement of the care process (Grimshaw 2006, Grol 2001, Lugtenberg 2009). The

implementation of guidelines improves their application, and this results in a proven improvement in health care outcomes (Grimshaw, 2004). It has also been shown that endpoints improve at the patient level, such as reduction in mortality and morbidity (Sellier et al. 2006, Menendez et al. 2005, Peterson et al. 2006, Stork et al. 2008, Wigmore et al. 2007, Heart 2006, Daly et al. 2006, Wroy et al. 2006).
Between 1987 and 2007, 33 reviews were conducted on the effectiveness of Directive implementation, which are summarized by Prior (2009). Unfortunately the reviews were based on low quality studies, so the results of the reviews are varied. Prior does not make a pooled analysis, but rated the reviews on quality. The two best methodological reviews show that interactive education (educational outreach) and audit & feedback methods are effective. In addition, reminders (during consultation) are in most cases also effective in bringing about change. Multi-faceted implementation did not appear to be substantially better than an individual strategy in this review (Jamtvedt 2006, Grimshaw, 2004).
It is clear from the literature that traditional education and dissemination alone are not sufficiently effective as an implementation strategy. The impact of mass media, patient information and financial incentives have not yet been sufficiently investigated (PRIOR, 2009).

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