Prenatal Detection of Oral Clefts

Diagnostic, genetic and ethical aspects

Wiesje Maarse

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Layout: Nicole Nijhuis, Gildeprint, The Netherlands
ISBN: 978-94-6233-028-3

This thesis was (partly) accomplished with financial support from the Department of Plastic, Reconstructive and hand surgery University Medical Centre Utrecht and Wilhemina's Children hospital, the Dutch Society of Plastic Surgery, ABN Amro, Allergan B.V., AllweCare medical B.V., BlooMEDical Benelux, Chipsoft B.V, Dalton Medicare B.V., Emdaplast, Examvision, Handencentrum Utrecht, Kwaliteitsinstituut van Medisch Specialisten, Mediplast, Quamedical, van Wijngaarden Medical, Junior Vereniging Plastische Chirurgie

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Diagnostic, Genetic and Ethical Aspects

Prenatale detectie van schisis

Diagnostische, Genetische en Ethische Aspecten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 27 augustus 2015 des middags te 2.30 uur

door

Wiesje Maarse

geboren op *17 augustus 1984*

te Nijmegen

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CONTENTS

1

General introduction and outline of the thesis

Since the introduction of standard prenatal screening in the Netherlands by means of ultrasound in 2007, parents can be confronted with a child with a cleft lip and/or palate already during pregnancy. As a consequence, this brings up the necessity for accurate counseling. When informing parents on outcome and prognosis of orofacial clefts it is crucial to understand its epidemiology, embryology, pathophysiology and treatment.

Epidemiology

Oral cleft is a congenital malformation that can involve the lip, palate, nose and underlying bony framework in various severities, and is the most common craniofacial anomaly considering the incidence of approximately 1:700 births[1]. The frequency of cleft lip with or without cleft palate varies across race and sex, with an incidence as high as 1:450 births among Asian and Native American populations, 1:1,000 among Caucasian populations, and 1:2,000 among African American populations. In contrast, in isolated cleft palate there appears to be no such heterogeneity with an incidence among races of about 1:2,000 births[23]. Boys are twice as likely to be affected compared to girls, whereas this relationship is reversed for isolated cleft palate[4, 5]. A unilateral lip occurs twice as frequently on the left side versus the right side and is nine times more common than a bilateral cleft lip [5, 6]. Unaffected (i.e., noncleft) parents who have one child with an oral cleft have an estimated recurrence risk of 4%, which rises to 9% with two affected children. An affected individual, has a 4% chance to become parent of a newborn with an oral cleft, with an increasing chance up to 17% if there is already an affected child [2, 7]. Recurrence increases with the severity of the cleft[8].

Oral clefts can be isolated, but are often associated with other congenital anomalies [9]. Studies on associated anomalies in newborns with oral cleft report variable rates, also since different definitions are used, encompassing anomalies as only major non-facial congenital anomalies to all anomalies, including minor[10]. Despite these differences, it is evident that the prevalence of associated anomalies is related to the cleft category, of which only cleft lip shows a lower prevalence of associated anomalies in comparison to cleft lip with palate or cleft palate only [11-15].

Embryology

The basic morphology of the face is established between the 4th and 10th week of human development. At five weeks' gestation, when the embryo is 3mm long, the ectoderm in the vicinity of the neural plate folds itself to form the neural tube. Special neural crest cells of ectodermal origin differentiate to form a special ectomesenchyme. Migration of the latter over and around the head is essential for the development of five facial prominences surrounding the primitive oral cavity[16]. A as a result of fusion of these five, namely the midline frontonasal prominence, two paired prominences, the maxillary and mandibular prominences, form the face (figure 1). The mesenchyme in the frontonasal prominence covers the forebrain (prosencephalon) and arises from neural crest cells derived from the midbrain (mesencephalon) and forebrain, whereas the maxillary and mandibular prominences are part of the first pharyngeal arch, and receive contributions from both the midbrain and hindbrain (rhombencephalon)[17].

The development of the upper lip begins during the 4th week of gestation and is completed by the 7th week[18]. On the frontonasal prominence two bilateral ectodermal thickenings are formed which invaginate to develop an oval nasal pit, hence dividing the frontonasal prominence into a lateral and medial nasal process. Simultaneously, in the 5th week the paired maxillary prominences enlarge and push forward by growing ventrally and medially. During the 6th week, the medial nasal processes migrate to each other and fuse to form the primordium of the bridge and septum of the nose. By the end of week 7, the inferior tips of the medial nasal process fuse in the midline and form the intermaxillary segment. From this intermaxillary segment, the nasal tip, columella, philtrum, labial tubercle, frenulum and primary palate are derived. The maxillary prominences give rise to the upper jaw and the sides of the upper lip and the mouth is reduced to its final width when fusion of the latter with the lateral portions of the mandibular prominences. Lastly, the mandibular prominence forms the mandible and lower lip to complete the oral aperture.

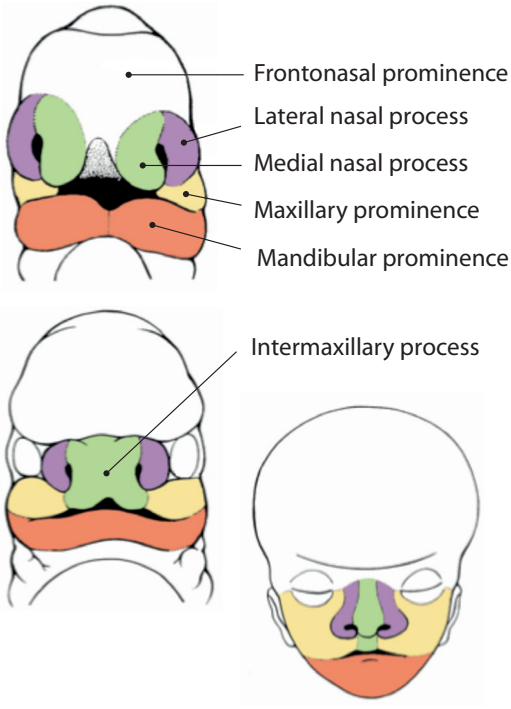

Figure 1 *This figure was published earlier in Larsen's human embryology, Gary C. Schoenwolf, Page 565, Copyright Elsevier 2009 and reprinted with permission of Prof. Schoenwolf who provided the figure.*

The secondary palate fuses later than the primary palate and is formed by the lateral palatal shelves, which are derived from the medial walls of the maxillary prominences. At first, these shelves grow downward, parallel to the lateral surface of the tongue. The tongue descends by forward growth and lowering of the mandibular prominences, allowing palatal shelve elevation. At the end of the 7th week, the shelves rotate rapidly into a horizontal position and then fuse with each other and the primary palate. This fusion proceeds from anteriorly, right behind the incisive foramen, to the posterior, thereby separating the nasal and oral cavities. The nasal septum, originates from the frontonasal prominence and grows simultaneously downward to fuse with the primary and secondary palate along the midline [17].

Facial clefting is the result of failure of both growth and fusion of the facial prominences anywhere. More specifically, failure of fusion of the intermaxillary process and maxillary prominences gives rise to a cleft of the primary palate including the lip, alveolar

process, and the hard palpate anterior to the incisive foramen, which notably can occur on either or both sides. Disruption of the confluence between the two palatal shelves results in a cleft of the secondary palate. Moreover, cleft palate may occur as secondary to mandibular dysplasia, in which the first pharyngeal arch is not developed appropriately. As a consequence, the tongue will not be lowered and will physically obstruct palatal shelve elevation. This form of secondary cleft palate resulting from a smaller mandibula (micrognathia) and accruing with glossoptosis (backward displacement of the tongue) in combination with often respiratory failure is referred to as Robin sequence[17, 19].

Although cleft lip and palate often occur simultaneously, the two defects differ in distribution with respect to sex, familial association, race and geography as mentioned earlier. Moreover, and as discussed above they differ on an embryological level in the fusion process, namely fusion of the intermaxillary segment with the maxillary prominences versus the fusion of the palatal shelves. Therefore, the cleft lip and cleft palate probably have a different etiology [17].

Midline or median clefts arise due to incomplete merging of the medial nasal processes which form the intermaxillary segment. These are part of holoprosencephaly, which includes a spectrum of forebrain development defects [17]. Together with atypical or craniofacial facial clefts they are rare and should be considered as separate craniofacial anomalies because of the different pathogenesis [20-22].

Pathology and related functional issues

A cleft can either be unilateral or bilateral and demonstrate a variable expression pattern, including microform, minor, incomplete and complete forms. In addition, they occur in a diversity of bone, cartilage and soft tissue deficiencies, thereby representing different functional problems. Microform cleft lip is an anomaly formerly termed "formefruste" and represents the most minor of cleft lip deformities. It manifests as a vermillion notch that is less than 3 mm in height compared with the Cupid's bow of the noncleft side, without a nasal deformity. A minor cleft lip is characterized by a vermillion notch greater than 3 mm combined with a vertical depression above the

notch into the nasal sill, a variable degree of nose deformity, and possibly a cleft of the alveolus [23]. Usually, these minimal clefts of the lip require surgical treatment, if not for aesthetics of the lip then for restoration of the underlying disruption of the orbicularis oris muscle.

An incomplete cleft lip has a variable degree of separation but by definition has an intact nasal sill, commonly referred to as Simonart band. A complete cleft lip extends through the nasal sill and floor and may or may not extend to the underlying alveolus and palate. A bilateral cleft lip can present as a combination of any of the above [24]. In a complete bilateral cleft lip and palate the prolabium and premaxilla, both derivatives of the intermaxillary process remain entirely separated from the lateral lip and maxillary arch elements as they fuse with the maxillary prominences[25].

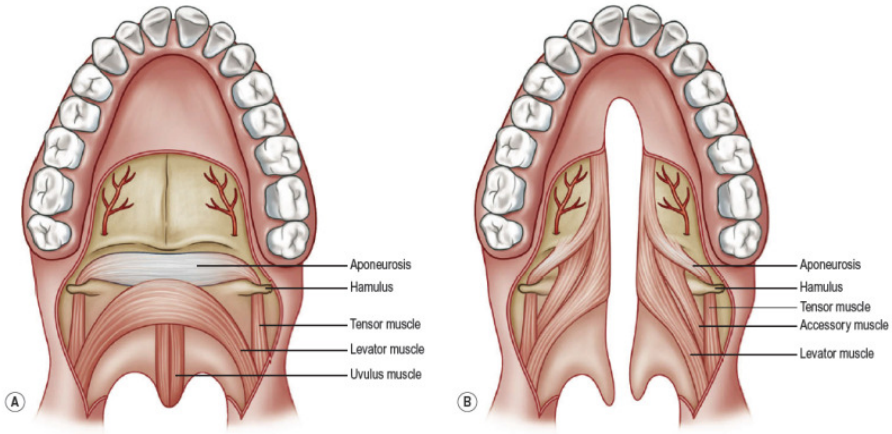

Figure 2 *This figure was published earlier in Plastic Surgery, Peter C. Neligan, Volume Three, William Y. Hoffman, Cleft Palate, Page 786, Copyright Elsevier 2013*

The musculature of the cleft velum is abnormal (figure 2B). Normally, the levator veli palatine muscle forms a transverse sling across the posterior half of the soft palate and contraction causes the soft palate to move superiorly and posteriorly, thus contacting the posterior pharyngeal wall for velar closure. Being discontinued in a cleft palate, the levator muscle runs more or less longitudinally along the cleft margin before it inserts aberrantly into the posterior border of the hard palate [26-28]. This results in ineffective contraction and inability to close against the pharyngeal wall, which in turn

can result in air escape through the nose and difficult speech. In addition, aberrant levator positioning as well as an abnormal fusion with the tendon of the tensor veli palatine muscle is thought to impair the function of the tensor muscle in assisting Eustachian tube function and is presumed to be contributory to cleft otopathology. Finally, there can be a submucous cleft palate presenting as the classic triad of bifid uvula, midline notching of the posterior hard palate in combination with diastasis of the velar musculature [29].

Besides the aesthetic complications of oral cleft there are functional problems related to the abnormal anatomy. As briefly described above, the velopharyngeal insufficiency of the palate musculature together with possible lip incompetence and abnormal dental position complicates normal speech. Furthermore, the incidence of otitis media effusion has been found to be present in 96-100% of cleft patients[30] which can lead to chronic obstruction and hearing disability on the long term. Children with oral cleft also have an increased risk to develop feeding difficulties[31]. For oral intake there are two separate activities necessary, namely generation of negative intraoral pressure and swallowing. To create negative pressure lips close anteriorly and the velum seals the pharynx posteriorly, both requiring an intact upper lip and palate. The failure of velopharyngeal closure is the basis of problems concerning breast-feeding and the need for a special Haberman feeding-bottle in newborns. Swallowing on a different note involves complex neuromuscular interaction of the tongue and pharynx. Children with oral clefts generally do not have difficulty with swallowing and aspiration unless intrinsic muscular abnormality of the tongue and pharynx is present. When a cleft palate is present food may reflux into the nasal cavity. Feeding problems can have adverse effect on growth[32], can lead to aspiration[31] and may also have negative impact on maternal attachment[33].

Lastly, 25-30 % of the oral cleft patients will develop severe midface retrusion because of insufficient maxillary growth, resulting in the typical deformity of class III malocclusion and many other dentofacial deformities [34]. Because of anatomical abnormalities of the nose, such as a deviated septum and structural deformities of the nasal cartilages, there are also functional airway and aesthetic problems. Approximately 60% of the patients have difficulty breathing through the nose[35].

Classification

The modified Kernahan[36, 37] model attempts to classify different types of oral cleft (figure 3). The upper limbs represent right and left sides of the primary palate, that is the lip, the alveolus, and the hard palate anterior to the incisive foramen. The lower limb represents the hard and soft palate posterior to the incisive foramen, either on the right or left side. In this modified Y classification, each right or left limb is assigned a number, 1-5 or 11-15 for the primary palate and 6-9 or 16-19, for the secondary palate, with 10 being a submucous cleft palate

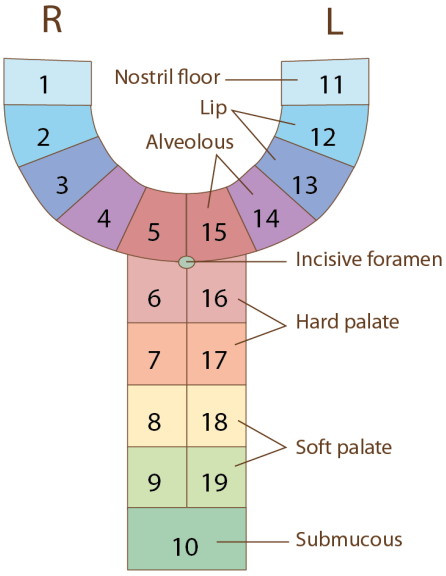

Figure 3 *Modified classification of Kernohan. Copyright by Ingrid Jansen.*

Treatment

A multidisciplinary approach is essential for satisfactory treatment of cleft patients[38]. Such approach encompasses a team of plastic and oral maxillofacial surgeons, orthodontists, speech pathologists, otolaryngologists, dentists and psychologists. Many different approaches exist for the treatment of oral cleft depending on the extent of the cleft. To date, no generic protocol has been recognized by the medical community as a whole, although there is a general consensus in Europe to close the lip during the first operation and the soft palate around 12 months of age, either together with the hard palate or as a two-stage palatoplasty[39],[40, 41]. When mentioning

surgical correction, the ultimate goal is to reconstruct a symmetrically balanced lip and nose, with good columellar length and repair of the orbicularis muscle. The aim for cleft palate repair is to create an anatomically intact and functional palate to optimize feeding, achieve normal speech and minimize maxillary growth restriction[25].

Presurgical, nasoalveolar molding, is a technique to facilitate surgical closure by preoperatively narrowing down the alveolar cleft [42]. This is combined with a nasal stent as outrigger to shape the alar cartilage into a more natural position [43-46]. Since cartilage is most flexible and moldable during the first weeks after birth[47], it is preferable to start nasoalveolar molding as soon as possible. Although nasoalveolar molding facilitates surgical closure and is beneficial for achieving nasal symmetry on short-term, the evidence is not substantial to support its effects on long-term outcome [48]. Opponents say the shape of the cartilage will relapse partially during the first year[42]. Others suggest that the necessary the frequent outpatient visits to adjust the device, necessary to optimize molding, is a burden to the family and leads to compliance failure[49].

A cheiloplasty for unilateral cleft lip is usually performed between 3 and 6 months after birth. "All cleft lip surgeons have their favorite surgical technique for repairing unilateral cleft lip. The operation is usually a hybrid of training experience and imagination" [50]. The ideal lip repair should approximate the medial and lateral lip elements at all levels (i.e. nostril sill, cutaneous roll, vermillion-cutaneus junction, and vermillion-mucosal junction) without interruption or loss of landmarks and achieve balance by providing length where tissue is short and excision where height is excessive[25]. The noncleft side heights provide the measures that must be created by the repair on the cleft side. The cleft side medial height will need to be lengthened and the lateral lip height will often need alteration to match that of the non-affected side. At the level of the cutaneous roll, the entire length of Cupid's bow should be preserved in the medial lip element. In the lateral lip element, Noordhoff's point should be preserved and used to form the base of the philtral column incision[51]. The cutaneous roll of the medial and lateral lip elements should be approximated in side-to-side fashion. Vermillion height deficiency below the cleft side half of Cupid's bow should be augmented and the red lip elements should be approximated with attention to creating a proper vermillion-mucosal junction [25].

To achieve these goals many different techniques have been described (figure 4). Rose [52] and Thompson [53] each achieved modest length in the repair by approximating curved and angled excisions, respectively. Mirault[54] used a low triangular flap from the lateral lip to increase length. Although this repair ignored Cupid's bow, it introduced an important principle that has been adopted by most techniques that followed; any substantial medial lip deficiency needs to be augmented with tissue from the lateral lip [25]. The inferior triangle repair of Tennison [55] using a Z-plasty became next. In the rotation-advancement repair by Millard [56], a curvilinear incision is made in the medial lip element. Mohler[57] altered the markings of the rotation-advancement repair to yield a scar that is more symmetric with the noncleft side philtral column. Straightening the curve of the rotation incision and extending the incision into the columella effectuated this alternative. The advantage of this technique is a more anatomically positioned scar. However, as with all rotation-advancement techniques it shares a necessary compromise of transverse lateral lip length when the lateral lip is vertically short. Noordhoff [58] as well as Fisher [51] introduced a small triangular flap from the lateral lip to fill the defect that arises when a small opening cut is made above the cutaneous roll on the cleft side of Cupid's bow to lengthen the lip.

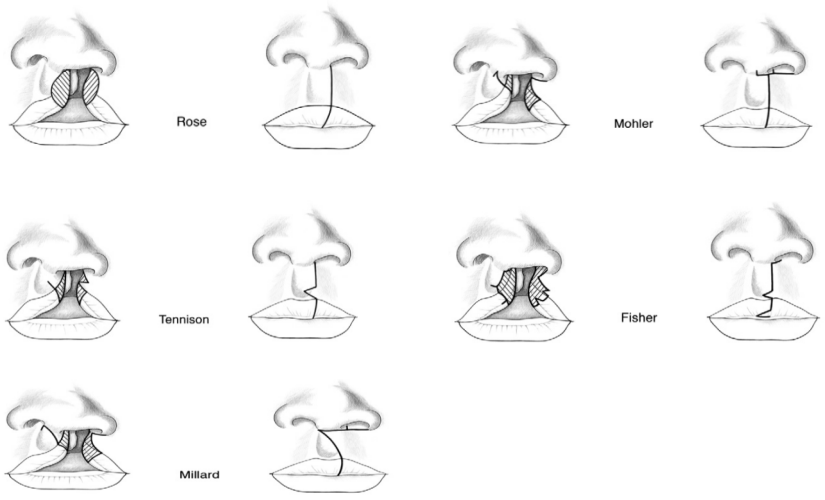

Figure 4 *Reprinted from, Vol 64/ed, Joshua C. Demke, Sherard A. Tatum, Analysis and evolution of rotation principles in unilateral cleft lip repair, Pages No. 313-318, Copyright 2011, with permission from Elsevier.*

The timing for closure of the palate is still under dispute. Since the driving force for palatoplasty is development and achievement of normal speech, most would agree that best results are correlated with closure near the time of the infant's language acquisition, which is before 12 months of age in the normal developing baby [59, 60]. Besides closure and lengthening of the palate to minimize postoperative velopharyngeal insufficiency, other aims of cleft palate repair are to minimize maxillary and alveolar growth disturbances and prevent fistula formation. The closure of a cleft palate is known to alter normal facial development[61]. When comparing patients with uncorrected cleft palate to corrected patients there is a significant reduction in maxillary sagittal length, retrusion, and maxillary dental-arch width in the uncorrected group [62, 63]. Another controversial subject of surgical repair is the timing and number of stages used. Several authors argue that flap elevation damages the periosteum and subsequent postsurgical scarring negatively impacts maxillary growth, something that could be minimized using two-stage approach with delayed repair of the hard plate [64-66]. However, proponents of early single-stage repair maintain that early closure improves speech outcomes through promotion of proper phonetic development and that improved speech outcomes outweigh potential growth restriction that may ensue [67, 68]. Finally, there is ongoing discussion on what type of technique to use for closing the secondary palate. A recently published trial [69] showed that a Furlow double-opposing Z-plasty compared to a von Langebeck palatoplasty with intraveloplasty results in improved velopharyngeal function. A disadvantage of the Furlow technique is that length is achieved at the expense of lateral tightening [25]. In order to maximize results after surgery postoperative speech therapy is essential, regardless of the technique used to close the palate.

If there exists an alveolar cleft, this must be treated for stable bone continuity of the maxillary arch, stable environment and bone support of erupting teeth, piriform bone support of the nasal base besides for separation of oral and nasal cavities. An alveolar cleft is associated with variable anomalies in dental development that must be taken into consideration with timing of surgery, technique and postsurgical orthodontic planning [70]. Management protocols differ but always comprehend a combination of orthodontic treatment and bone grafting, mostly before eruption of the adult cleft

canine side. Nowadays bypassing or enhancing autologous bone grafting by means of tissue engineering solutions has become an important topic in alveolar cleft grafting. Replacement of the autologous bone graft will result in absence of donor site morbidity[71]. By closure of the lip, palate and alveolar grafting all the surgical steps in basic cleft care are taken. Afterwards the treatment becomes more individualistically driven. Moreover, during this phase of treatment patients have reached an age at which they can influence their own treatment. Orthognatic surgery and secondary lip corrections as well as rhinoplasty after adolescent growth spurt are frequently needed to improve aesthetics, dental occlusion and airway function of the nose[72, 73].

In conclusion, the course of oral cleft treatment is complex and spans often the entire childhood, adolescence and adulthood. Although much of the primary management of patients is surgically driven and focusing on function, the overall goal of treatment includes also psychosocial and social wellbeing of the patient and his/her family. An oral cleft that involves the nose and lip imposes evident facial differences and is therefore expected to have impact on social interactions and quality of life [74]. Overall, the majority of children and adults with an oral cleft do not appear to experience major psychosocial problems [75], although disturbances have been observed such as behavior problems, anxiety, depression, aesthetic dissatisfaction with facial appearance in both children and adults [76]. The treatment of children with oral cleft is continuously evolving, but current techniques and treatment protocols generate excellent functional and aesthetic results and prognosis, with most studies reporting high rates of treatment satisfaction [77, 78].

Introduction of prenatal screening

Since the introduction of standard prenatal screening, oral clefts are being diagnosed on prenatal ultrasound. Where formerly parents were confronted with a child with a cleft lip and/or palate at birth, nowadays they can are already be informed during pregnancy. In The Netherlands, transabdominal ultrasound screening at 20 weeks of pregnancy was made universally accessible by legislation and health insurance coverage in 2007[79]. The screening was aimed initially at Down syndrome, but the possibility for secondary screening for oral cleft and other congenital anomalies was

included as well. Consequently, this added a whole new dimension to cleft care. The changes in screening programme and related questions and concerns initiated the research for this thesis.

In 1981, Christ and Meininger[80] were the first to report the detection of a cleft lip and palate deformity on ultrasound. Ever since, detection rates increased from approximately 5% in the early 1980s to over 26% in the late 1990s [81] and have increased to about 23-58% in most recent prospective studies [82, 83]. Subsequently, there is a need for accurate information to aid in prenatal counseling. When informing parents on outcome, prognosis and treatment the type of cleft as well as the presence of other congenital anomalies are crucial information. Furthermore, in clinical practice there is often the discussion whether further invasive tests should be offered prenatally to identify chromosomal defects. This will in turn influence counseling and management of the pregnancy significantly [15]. However, the reported rates of associated anomalies in prenatal cleft populations vary greatly among reported studies [12-14, 82].

In response to increasing prenatal detection rates of oral cleft, the cleft lip and palate team of the Wilhelmina Children's Hospital in Utrecht set up a prenatal cleft clinic to participate in counseling. Parents meet here with an obstetrician, plastic surgeon and a medical physiologist of the team. The etiology and pathogenesis of an oral cleft are then explained as well as the medical, surgical and psychosocial needs of a child with a cleft lip and possible cleft palate. Although former studies have concluded that most parents prefer to know the diagnosis prenatally rather than at birth [84-87], the effect of counseling has never been evaluated prospectively during pregnancy. Former studies assessing the impact of a prenatally detected oral cleft are of retrospective design, implying that at the time of assessment the child was already born. This could affect a parent's view on the impact of an oral cleft diagnosis. Potential advantages of prenatal cleft diagnosis were formulated by Johnson and Sandy [88], including psychosocial preparation, opportunity for parent education, planned neonatal care, anticipation on possible feeding problems as well as increased reproductive awareness can be maximally exploited. On the contrary, there may be emotional disturbance of the pregnancy [84] and more importantly the concern of increasing numbers of termination

of pregnancy (TOP) of fetuses with an isolated oral cleft. The latter concerns were raised by reports from Israel were numbers of TOP for oral cleft reach more than 95%[89].

Influences on the decision making process of parents expecting a child with an oral cleft have been discussed in several expert opinions. The 'perception of burden' of an oral cleft and the possible stigmatization of a 'less-than-perfect' child have been described [90]. It has been shown that a dedicated cleft team can educate parents in order to prepare them optimally and reduce the anxiety associated with the diagnosis of a fetal malformation [91]. Other studies assessing a woman's decisions after diagnosis with an abnormality other than oral cleft revealed considerations like the severity of the abnormality and its visualization on ultrasound scan [92-95]. In addition, influences of the caregiver who counsels the couple [96], the 'child's best interest' and economic issues have been described with respect to parents' decisions [97]. The aforementioned ambiguities led to formation of research.

Outline and aims of this thesis

The purposes of this thesis are to obtain more knowledge on the accuracy of ultrasound screening and the incidence of associated anomalies besides an oral cleft. In addition, the aim is to obtain more insight into opinion of professionals as well as the psychosocial, and moral aspects in thoughts and attitudes of parents expecting a child with an oral cleft.

The first part of this thesis focuses on the classification of oral cleft. In **chapter 2,** a new prenatal oral cleft classification is defined in order to improve uniformity between ultrasonographers in daily practice. In part two, the introduction and accuracy of screening for oral cleft is covered. In **chapter 3** the Dutch routine screening system for physical congenital anomalies is described, with a focus on oral cleft. The diagnostic accuracy of oral cleft by ultrasound is assessed in a systematic review in **chapter 4**, besides in a prospective study in **chapter 5**. The precision of prenatal ultrasound in determining the type of oral cleft is described in **chapter 6**. Since oral clefts are being diagnosed prenatally more frequently, there is the need for more accurate information on the risk of associated anomalies and chromosomal defects. In **chapter 7** a systematic review was conducted to investigate the prevalence of associated anomalies per

type of cleft, which can aid prenatal counseling. Part three of the thesis addresses to prenatal counseling op parents expecting a child with an oral cleft. Different factors are thought to influence parental opinion on oral cleft, one of them being the obstetric care provider's attitude. In **chapter 8** the providers' opinions about oral cleft and possible termination of pregnancy for isolated oral cleft are compared between Israel and The Netherlands. Israel was chosen for comparison because of high rates of TOP for isolated oral cleft. In **chapter 9** we obtained insight into the psychosocial and moral considerations of prospective parents concerning oral clefts, the burden of oral clefts and parents' attitude toward possible termination of pregnancy. Finally, in **chapter 10** three types of counseling are discussed, informative counseling, shared decision making and paternalistic counseling, to agree on which type of counseling is the most appropriate for cleft lip and palate teams. This thesis is completed by a general discussion and implications for further research in **chapter 11**.

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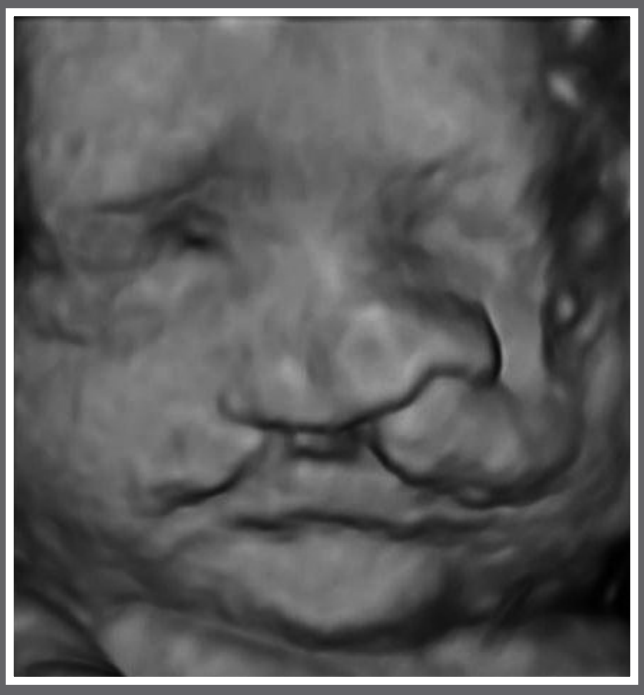

Part I
Classification of Oral Cleft

2

A practical prenatal ultrasound classification system for common oral clefts

Prenatal Diagnosis, 2015 Jun 10. [Epub ahead of print]

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ABSTRACT

Objective To introduce and validate a new oral cleft classification system based on prenatal ultrasound for use by professionals in daily practice.

Methods During a three-year period (2011-2014), all cases of prenatal oral cleft diagnosed by ultrasound were retrospectively reviewed. A new prenatal ultrasound classification system was introduced. For the purpose of validation, prenatal ultrasound images of oral cleft types were described according to the new classification system and were compared to postnatal findings by reviewing medical records.

Results A total of 103 fetuses with oral cleft were identified by ultrasound. The mean gestation time at detection was 20.4 weeks (95% CI: 20.0-20.7). The association between oral cleft and other anomalies varied by cleft type; types 2b/3b and 4 were most frequently associated with other anomalies. The measure of agreement between the prenatal and postnatal findings showed a Kappa value of 0.63 (95% CI: 0.52-0.75), demonstrating the accuracy of this new classification system.

Conclusion A new prenatal oral cleft classification system is presented. This system appears to be accurate, and it shows the variation in the risk of associated anomalies for each cleft type. We expect that ultrasonographers will be able to use the new classification in daily practice.

INTRODUCTION

Oral cleft (OC) is the most common congenital facial malformation; it occurs in approximately 1 of 700 live births[1]. Transabdominal ultrasound (US) prenatal screening is the standard of care in most Western countries, resulting in an increased frequency of prenatal OC diagnoses[2, 3].

Several postnatal classification systems for OC have been described in the literature, all of which have aimed to simplify the diversity and complexity of cleft lip and palate anomalies based on embryologic and anatomic principles[4, 5, 6]. An accurate OC diagnosis is essential because different types of cleft are associated with specific risks of anomalies and chromosomal disorders[7]. Moreover, an accurate diagnosis is important because it correlates with the severity of the malformation, prognosis and outcome[8]. In practice, different types of OC have specific considerations in terms of aesthetic, functional (hearing, feeding, dentition, speaking) and psychosocial (construction of self-image and relational and attachment disturbances) outcomes[8].

Nyberg and colleagues[9] were the only authors to describe a US classification of OC, including five categories of clefts: type 1: cleft lip; type 2: unilateral cleft lip and palate; type 3: bilateral cleft lip and palate; type: 4 midline cleft lip and palate; and type 5: cleft associated with amniotic bands or limb-body-wall complex. However, this classification system has several shortcomings. First, cleft palate alone is not included. Second, the Nyberg classification does not differentiate unilateral versus bilateral cleft lip (and alveolus) alone. Third, in our opinion, types 4 and 5 should not be included in a prenatal US classification system because they are holoprosencephalic and atypical clefts (including a spectrum of forebrain development defects), respectively[10]. Such atypical clefts have a different embryologic pathogenesis and are rare compared to the more common paramedian clefting, such as those that Nyberg et al. classified as types 1-3[11, 12]. Another argument for omitting Nyberg types 4 and 5 is their rare incidence in combination with the high lethal outcome associated with most median cleft types[13]. In conclusion, the prenatal classification of Nyberg is incomplete and does not match postnatal classifications. Thus, the aim of our study was to define a

new prenatal OC classification, based singularly on structural/anatomic findings, using a practical approach that can be easily applied by every professional performing prenatal fetal anomaly scans.

EMBRYOLOGY

Thorough knowledge of embryological development in the craniofacial region can help ultrasonographers to understand and distinguish among different types of OC. Facial clefting is the result of a disturbance in both growth and fusion during basic facial morphology development between the 4th and 10th weeks of human development and involves five facial prominences[14]. As a result of fusion of the midline frontonasal prominence and the two paired prominences (i.e., the maxillary and mandibular prominences), the face is formed (Figure 1). On the frontonasal prominence, two bilateral ectodermal thickenings form to invaginate as an oval nasal pit, dividing the frontonasal prominence into a lateral and a medial nasal process. By the end of the 7th week of gestation, the inferior tips of the medial nasal process fuse along the midline and form the intermaxillary segment.[10] Failure of the intermaxillary process and the maxillary prominences to fuse from posterior to anterior results in clefting of the lip, alveolar process, and hard palate anterior to the incisive foramen (primary palate). Such clefts are therefore always paramedian clefts and are termed unilateral or bilateral cleft lip, in some cases including the alveolus and primary palate.

The secondary palate, which is located dorsally to the incisive foramen, fuses after the primary palate and is formed by the lateral palatal shelves, which are derived from the medial walls of the maxillary prominences. The fusion process normally starts directly behind the incisive foramen in the middle and extends anteriorly to posteriorly, ending with the uvula, which is indicative of a closed soft palate[15]. Disruption of the confluence between the two palatal shelves results in a cleft of the secondary palate. A secondary cleft palate can occur simultaneously with clefting of the lip and primary palate. However, cleft palate only can also occur as a consequence of mandibular dysplasia, in which the first pharyngeal arch does not develop appropriately. In such cases, the tongue will not be lowered and will physically obstruct palatal shelve elevation[10]. This secondary cleft palate type, resulting from a small mandible (micrognathia)

and accruing with glossoptosis (backward displacement of the tongue), often in combination with respiratory failure of the newborn, is referred to as Robin sequence[10, 16]. Submucous cleft palate presents as the classic triad of bifid uvula, midline notching of the posterior hard palate and diastasis of the velar musculature of the soft palate[17]. True median cleft, which can be detected on an anomaly scan, is a form of median craniofacial dysplasia. These cases can be classified based on tissue agenesis and holoprosencephaly at one extreme (hypoplasia) and frontonasal hyperplasia and excessive tissue (hyperplasia) at the other extreme; median anomalies with clefting and normal tissue volume (dysgraphia) occupy the middle of the spectrum[13]. Defects in the medial nasal prominence, which is closely associated with forebrain development, result in abnormal development (dysplasia) and therefore present a different pathogenesis than paramedian clefts[13, 11, 12]. Hence, median clefts were not included in the classification system presented here. For more information on median craniofacial dysplasia, refer to Allam et al.[13]

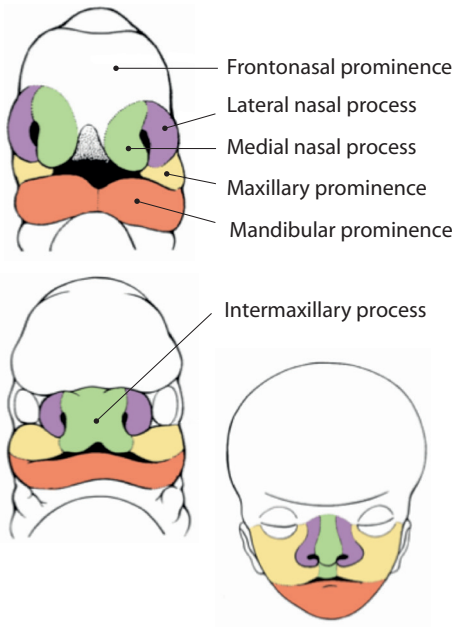

Figure 1 *This figure was published previously in Larsen's Human Embryology, Gary C. Schoenwolf, Page 565, Copyright Elsevier 2009, and is reprinted with permission from Prof. Schoenwolf, who provided the figure*

METHODS

Study design

In this retrospective study, between August 2011 and August 2014, all prenatally diagnosed cases of OC in the Fetal Medicine Unit of the Wilhelmina Children's Hospital were reviewed, including intra-uterine fetal deaths (IUFD) and cases in which the parents opted for termination of pregnancy (TOP). In the Netherlands, a fetal anomaly scan is offered to all pregnant women at approximately 20 weeks of gestation. If an anomaly is suspected, the mother is referred to a tertiary care center, such as Wilhelmina Children's Hospital, where a more detailed 2D/3D US is performed to confirm diagnosis. Postnatal diagnoses were used as the 'gold standard.' In the first week after delivery, a plastic surgeon and a clinical geneticist from the cleft and palate team examined these newborns to verify the prenatally diagnosed cleft type. Accordingly, the medical records of the cleft and palate team were used as reference to compare the prenatally and postnatally diagnosed types of OC.

For the purpose of prenatal screening, the Netherlands is subdivided into eight regions in which trained midwives, ultrasonographers and obstetricians perform anomaly scans, including detailed facial examinations. Referred women or children from other regions were excluded to prevent spectrum bias in the detection rate[18]. This study was approved by the Medical Ethical Committee at the University Medical Center Utrecht.

Statistical analysis

Data analysis was performed using descriptive statistics (i.e., frequencies or means). To study the agreement between the pre- and postnatal diagnoses, the Kappa statistic was calculated. This study was not designed to address to false-negatives and – positives findings, but to show reliability of identification of a certain type of OC with a fetal scan. Confidence intervals (CI, 95%) were calculated using bootstrapping, for which we replicated the analysis 1000 times with random replacement samples. Analysis was performed with SPSS version 20.0 (Ref: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

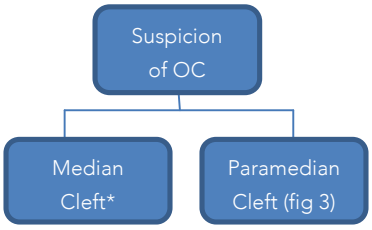

Figure 2: *Algorithm for suspicion of OC (Oral Cleft)* median cleft is excluded from our classification because of:* a. *Different embryologic pathogenesis* b. *Rare incidence* c. *High lethal outcome*

Classification

The new US classification provides an overview for the most common types of OC, as explained before median cleft was excluded. On ultrasound a median cleft becomes evident when no protruding premaxilla is present in profile. A diagnostic algorithm for suspicion of OC was presented in figure 2. Our classification system is adapted from a modified Kernahan postnatal classification system[19] (Figure 3). This classification system describes all common types of OC using symbols. A double Y, similar to the shape of the maxilla and its vertical arm, represents the palate. Thus, this system allows all OC components (i.e., the lip, alveolus, hard and soft palate, submucous palate) to be delineated; thus, this system indicates the degree of OC (Figure 4).

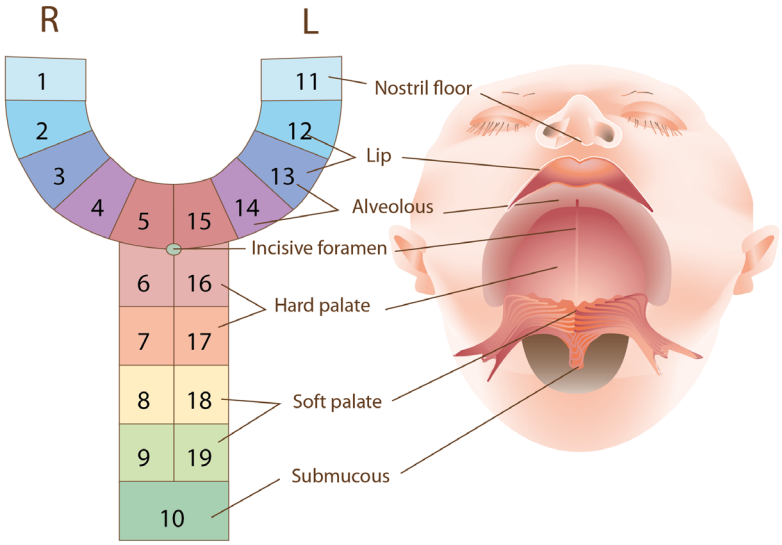

Figure 3 *Modified Kernahan's striped Y classification, with on the left all OC components (i.e., the lip, alveolus, hard and soft palate, submucous palate)*

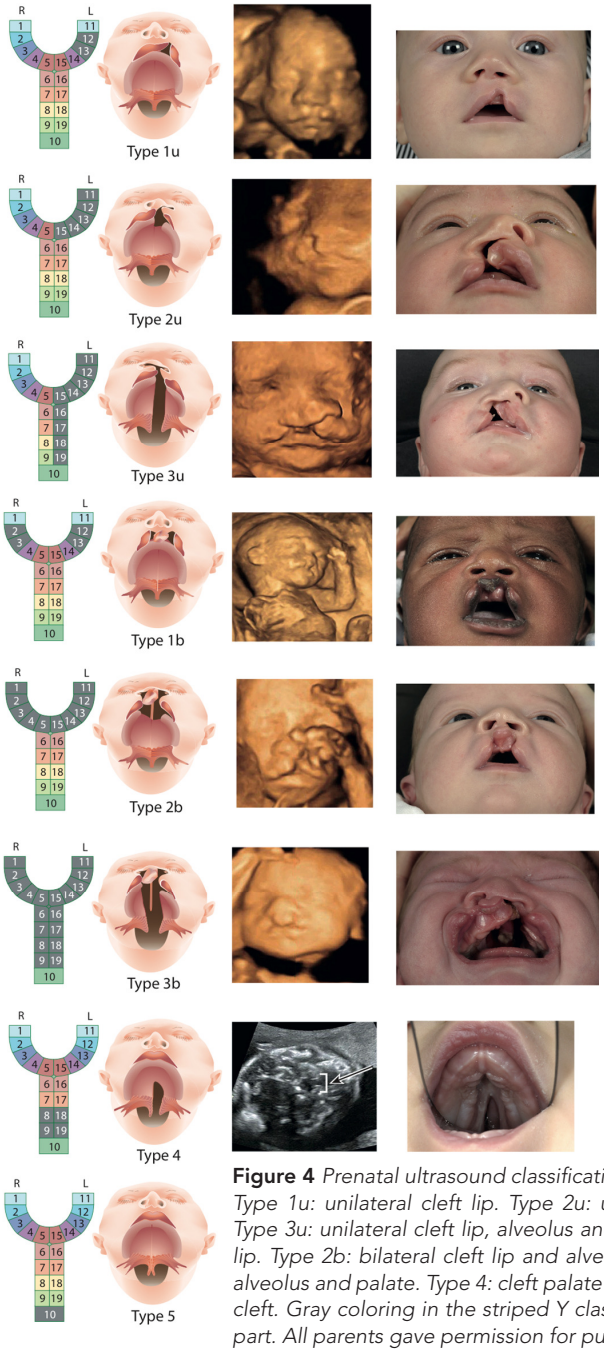

Figure 4 *Prenatal ultrasound classification: Type 1u: unilateral cleft lip. Type 2u: unilateral cleft lip and alveolus. Type 3u: unilateral cleft lip, alveolus and palate. Type 1b: bilateral cleft lip. Type 2b: bilateral cleft lip and alveolus. Type 3b: bilateral cleft lip, alveolus and palate. Type 4: cleft palate only (arrow). Type 5: submucous cleft. Gray coloring in the striped Y classification indicates the affected part. All parents gave permission for publication.*

RESULTS

In total, 103 fetuses with an OC were identified by US. In one case, a type 4 cleft (cleft palate only) was diagnosed at 20 weeks of gestation but was not confirmed at birth; this case was the only false positive in the study (1/103 = 0.97%) and was excluded from the study. The mean gestation time at detection was 20.4 weeks (95% CI: 20.0-20.7).

Associated anomalies

Of the 102 fetuses that were prenatally diagnosed with OC, 77 (75.5%) were isolated cases and 25 (24.5%) had associated anomalies (Table 1). The incidence of associated anomalies differed by cleft type: 9.1% (2/22) in type 1u, 17.4% (4/23) in type 2u, 16% (4/25) in type 3u, 0% (0/1) in type 1b, 33.3% (1/3) in type 2b, 30% (6/20) in type 3b, and 100% (8/8) in type 4. No type 5 OCs were diagnosed during the study period. Of the 25 associated anomalies, there were 12 cases with an abnormal karyotype (four cases of trisomy 13, two cases of trisomy 18, three cases of trisomy 21, one case of balanced translocation chromosomes 11 and 13, one case of duplication of chromosome 17p and one case of chromosome 4p deletion and 6q duplication). Seven syndromes were diagnosed (two cases of Walker-Warburg syndrome, two cases of Stickler syndrome, one case of Wolf-Hirschhorn syndrome, one case of Blepharo-cheilo-dontic (BCD) syndrome, and one case of Opitz G/BBB syndrome), and one case of Robin sequence was diagnosed. A comparison of these results with the postnatal findings revealed that the prevalence of the associated anomalies differed. This result can be explained by several different factors, including an incorrect prenatal diagnosis of the OC type (34 cases), having no description of the specific type of cleft with autopsy (seven cases) and having missed or incorrectly diagnosed the associated anomalies on the US scan (two cases). The prevalence of OC with associated anomalies postnatally was 6.7% (1/15) for type 1u, 16.7% (3/18) for type 2u, 18.8% (6/32) for type 3u, 0% (0/1) for type 1b, 100% (1/1) for type 2b, 28.6% (6/21) for type 3b, and 85.7% (6/7) for type 4, which totals 24.2% (23/95) for the associated OC.

Table 1 *Characteristics and prevalences of the associated anomalies by cleft type (prenatal and postnatal)**

	Total		Isolated		Associated		Chromosomal		Syndrome	
Cleft type	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1u	22	15	20	14	2	1	0	1	0	0
2u	23	18	19	15	4	3	3	0	1	1
3u	25	32	21	26	4	6	4	3	1	1
1b	1	1	1	1	0	0	0	0	0	0
2b	3	1	2	0	1	1	0	0	0	0
3b	20	21	14	15	6	6	3	1	3	3
4	8	7	0	1	8	6	2	0	2	2
Total	102	95	77	72	25	23	12	5	7	7

* Pre- and postnatal data are not similar due to several different factors, including incorrect prenatal diagnosis of the OC type (34 cases), no description of the specific type of cleft with abduction (seven cases) and missed or incorrectly diagnosed associated anomalies according to the US scans (two cases).

Validation of classifications

The prenatal findings by US were compared with the postnatal diagnosis (Table 2). In six TOPs and one postnatal death, the OC was confirmed (but not the specific type). Therefore, these cases were excluded for assessing the validation of the classification. The measure of agreement between these settings showed a Kappa value of 0.63 (95% CI: 0.52-0.75), indicating high accuracy. Prenatal diagnosis was correct in 68 of the 95 cases (71.6%). There were 22 cases (23.1%) in which the type of cleft was more severe than that identified by US. Two of these cases were bilateral instead of unilateral. Most commonly, the additional cleft palate was not correctly diagnosed (17/22). In five cases (5.3%), the postnatal diagnosis was less severe than that identified by US.

Table 2 *Prenatal versus postnatal diagnoses of oral cleft; bold numbers indicate a correct diagnosis**

	Postnatal findings							
Prenatal findings	**Type 1u**	**Type 2u**	**Type 3u**	**Type 1b**	**Type 2b**	**Type 3b**	**Type 4**	**Total**
Type 1u	**14**	5	3	0	0	0	0	22
Type 2u	1	**9**	10	0	0	2	0	22
Type 3u	0	4	**19**	0	0	0	0	23
Type 1b	0	0	0	**1**	0	0	0	1
Type 2b	0	0	0	0	**1**	2	0	3
Type 3b	0	0	0	0	0	**17**	0	17
Type 4	0	0	0	0	0	0	**7**	**7**
Total	15	18	32	1	1	21	7	95

* Seven cases were excluded because there were no descriptions of the specific type of cleft with obduction in cases of TOP or postnatal death.

DISCUSSION

The prenatal US classification system of OC we describe is based on embryology and although retrospectively conducted it appears to be accurate. Compared to the classification system presented by Nyberg et al.[9], the system presented here provides a more correct overview of the most common types of OC. Furthermore, in our classification system, isolated cleft palate is included and atypical clefts are excluded because the latter are based on a different embryologic pathogenesis, have high lethal outcome and rare incidence in comparison to common paramedian clefts. Accurate classification is essential because it not only reflects to the severity of the cleft but also is indicative of additional anomalies and/or chromosomal disorders, as shown in this study. Correct diagnosis is important to properly inform parents in a prenatal setting about the available treatment options as well as the aesthetic, functional and psychosocial consequences.

It is important to understand the shortcomings of predicting the type of OC with US. First, this was a retrospective study, thus the ultrasonographers were not blinded for the postnatal findings of the cleft lip and palate team, possible influencing the information about inter- and intra-rater agreement. A prospective study should be

performed to assess final reliable accuracy. Second, there are more variations in OC possible than those described in this US classification system. In addition to being unilateral or bilateral, OC demonstrates a variable expression pattern, including microform, minor, incomplete and complete forms. However, the US classification system used in this study aims to provide a practical tool for ultrasonographers to use in daily practice. Third, a submucous cleft (type 5) will likely never be diagnosed by US because the outer anatomy is normal. Submucous clefts are often diagnosed later in life, when children appear to have difficulty speaking. Because of the short follow-up period, the incidence of type 5 OC is not reliable. Fourth, isolated CP (type 4) is rarely diagnosed prenatally, although when type 4 is suspected, it is generally correct . Even when a cleft lip was diagnosed by US, visualization of the palate was difficult in several cases. Hence, when there is a suspicion of a cleft lip and alveolus, the parents should be told during counseling that there is a reasonable risk of an additional cleft palate (Table 1). This diagnosis can greatly alter the long-term prognosis for the child because it is commonly associated with difficulties in speech[20], feeding[21, 22], hearing[20], and postoperative mid-facial retrusion[23].

Recently, several studies have attempted to improve upon the detection of the cleft palate. Hassan et al.[24] described visualization of the tongue abutting the nasal septum in the transverse view as strongly indicating the presence of a cleft of the hard palate. Bäumler et al.[25] illustrated high diagnostic accuracy with 3D axial visualization of the hard palate. Furthermore, Wilhelm et al.[15] suggested the use of a novel marker for diagnosing clefts of the soft palate with the sonographic appearance of an 'equal sign,' referring to a normal uvula. An unremarkable uvula implies the presence of in intact palate because, as we explained in the embryology section, the palate closes from the anterior to the posterior. Several other techniques using three-dimensional US have been described, such as the reversed face view[26] and angled insonation[26]. However, it remains a great challenge to identify cleft palate alone without a cleft lip or micrognathia to alert the ultrasonographer to examine the fetal face in greater detail. Isolated cleft palate represents approximately one-third of the total incidence of OC[1]; therefore, it should have a place in prenatal classification systems.

CONCLUSION

This new prenatal US classification system offers a systematic and practical approach for prenatal screening of oral clefts and, unlike the system presented by Nyberg, provides a accurate correlation with the postnatal cleft diagnosis. The classification system presented here is based on a commonly used postnatal system; therefore, it will improve communication between obstetricians and cleft lip and palate teams. We expect that parental counseling in both fields will improve as a result of using this classification system.

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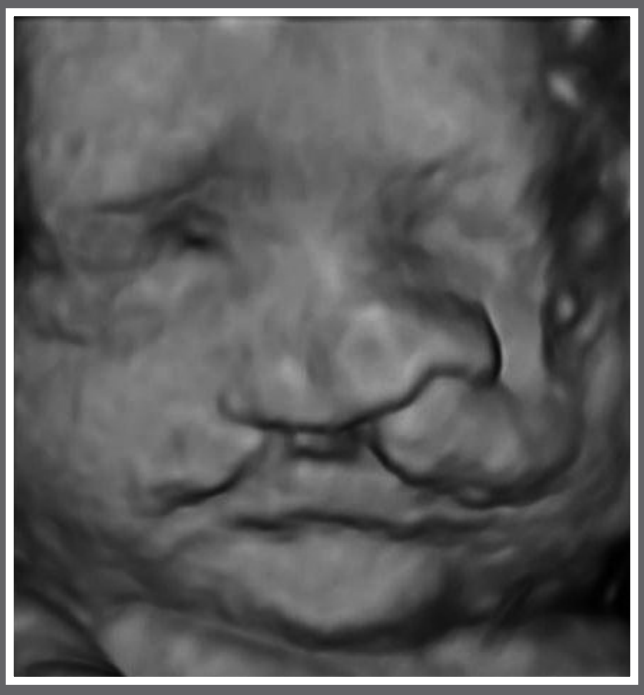

Part II
Screening for Oral Cleft

3

Prenatal Screening for Orofacial Clefts in the Netherlands: A Preliminary Report on the Impact of a National Screening System

Cleft Palate-Craniofacial Journal, March 2011, Vol. 48 (2) 183-9

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ABSTRACT

In the Netherlands a new and countrywide routine screening system for physical congenital anomalies was introduced by legislation in 2007. The screening was aimed initially at Down syndrome, but under specific conditions secondary screening for cleft lip and palate and other congenital malformations is performed as well. This article gives an overview of the Dutch system, with a focus on cleft lip (and palate) and the report of one center's experience. In general, voluntary termination of pregnancy in the second trimester has increased slightly since the introduction of the current system, but the termination-of-pregnancy rate for isolated cleft lip and palate remains limited in the Netherlands.

The technical progress in ultrasound (US) screening allows for ever-earlier and increasingly reliable detection of a diversity of physical congenital anomalies in the prenatal period, including cleft lip[1]. For this reason, high-resolution, transabdominal US examination has become the standard of care in many countries including the Netherlands. This development has led to new legislation in the Netherlands regarding prenatal US. In the Netherlands, the Population Screening Act (PSA)—enacted in 1996—allows the Dutch Minister of Health, Welfare, and Sport (HWS) to issue a permit for certain types of population screening. Since the enactment of the PSA, it is obligatory that the Minister of HWS consult the Health Council of the Netherlands before he or she issues a permit for such screenings. The task of the Health Council's committee on the PSA is to advise on the issue of permits for population screening. In October 2006 the Health Council wrote an extensive preliminary report advising the Minister of HWS[3], followed by a final report on the same subject focused on the screening for Down syndrome and neural tube defects[2]. Based on the preliminary advice in 2006 and the legal ramifications of the PSA, it was decided at the end of 2006 to encompass the medical technical innovations in the field of prenatal screening in new legislation, effective in 2007. It should be noted that the Netherlands was quite late in setting rules in this field because prenatal US was available for many years for individual parents at their own expense or for a medical reason. Any regulation for routine screening of all pregnant women was postponed because for a long time, the Minister of HWS defended the view that in general any diagnostic work should be performed routinely only when there were implications for treatment or prevention; the possibilities for prevention of or prenatal treatment for congenital abnormalities during pregnancy were judged minimal or absent. The introduction of routine prenatal US for all pregnant women, therefore, was considered an unnecessary luxury, only making health care more expensive, and was deferred for many years. This view of the Ministry of HWS was in accordance with the principles for prenatal screening programs as reviewed by Simopoulos[4]. However, the result of this policy was lack of transparency, with individual institutions, doctors, or other health care workers offering pregnant women a variety of prenatal screenings according to their own insights, sometimes covered by health care insurance and sometimes not. Equal access to the same quality of screening was no longer ensured. Pressure from the professionals in the field and

patients' platforms seeking standardization and uniform access slowly brought about a change of mind at the ministerial level. Next, the Ministry of HWS stipulated one uniform system for the whole country as prerequisite for any adjustment, and in 2006 the Minister of HWS asked the opinion of the Health Council about several proposals to improve the situation. The advice of the Health Council[3] induced the definitive change in policy by the government. According to the Minister of HWS, the focus of routine US screening in the Netherlands is not prevention and treatment. The screening was designed primarily to inform future parents about possible defects and their treatment options. Thus, the screening was never intended to improve the overall health at a population level. To the knowledge of the authors, the government performed no fundamental cost-benefit study for prenatal US screening in the Netherlands to support the change in policy in 2006.

The new legislation organizes prenatal screening in the Netherlands in detail. Important issues include the fact that Dutch health insurance companies were required to cover prenatal screening by US in their policies and that a new Central Organization for Quality Control and Data Acquisition of Prenatal Screening (Central Organization) was founded and funded. The health care insurance companies, the societies of the medical specialists involved, the society of general practitioners, patients' platform, and the regional referral centers are represented in this Central Organization. Its task is to ensure countrywide quality criteria, to draft uniform information to patients, to design a uniform database for the screening, and to ensure uniform protocols and uniform contracts with counselors and US diagnostic centers. The Central Organization was incorporated in the structure of the Rijksinstituut voor Volksgezondheid en Milieu (RIVM)[5], a government research institute for public health and a safe living environment in the Netherlands. Minimum quality criteria for counselors were set, and as a consequence, professionals can only be involved in the counseling for prenatal screening on the condition that counseling is done weekly as a routine part of their practice (minimum 50 per year). Similarly, quality criteria for persons performing the basic US screening (Structureel Echoscopisch Onderzoek) were drafted[6]. The RIVM provides a Web site with ample information on the subject, including all relevant documents in Dutch in pdf format and a useful version in English about the screening[5].

Ministerial permission to organize the screening was granted to eight regional nonprofit centers (trusts) in the Netherlands, specifically founded for this purpose. These trusts oversee the screening in their regions and engage sonologists, midwives, and obstetricians within their region to perform the screening. A contract for screening includes an agreement on the quality of the US equipment, experience, training, and continuing education of the person performing the US and the counseling. Information of each US screening will be collected directly (online) into a new countrywide database system. This information, together with the postnatal findings, should give the opportunity to provide important information about the quality of the US screening and its consequences in the future.

The average population covered by a regional referral center is about 2 million people, which translates to about 20,000 pregnancies annually per center. In order to reduce costs and to ensure easy access for women, the basic screening takes place at primary-care level, mostly by certified midwives or sonologists. In case of a suspected abnormality, the woman is referred to a certified obstetrician in one of the eight regional referral centers (or one of their satellites) for further analysis and counseling. Further analysis always includes advanced US screening. The standard for advanced US screening is set by the Dutch Society for Gynecology and Obstetrics and is available electronically[6]. So far, only transabdominal US is used for routine screening in the Netherlands.

The focus of the screening protocol is to identify fetuses with Down syndrome or neural tube defects[3]. Screening for Down syndrome entails a risk assessment based on the combination of maternal age, biochemical markers such as pregnancy-associated plasma protein A (PAPP-A) and the beta subunit of human choriogonadotropin (fbeta-hCG) in the blood of the mother in the first trimester of the pregnancy, and US measurement of the nuchal translucency between 11 and 14 weeks of gestation. To screen for neural tube defects an additional US is performed at 18 to 22 weeks of gestation. During the latter, a systematic screening of the whole body is done with a primary focus on neural tube defects. This particular screening enables detection of other birth defects, including orofacial clefts. Currently about 25% of the pregnant women participate in the Down screening and 95% of the women opt for the US at 18 to 22 weeks.

Informed Consent

All pregnant women are offered the option to obtain information about prenatal screening. They remain free in their choice whether to obtain the information and subsequently whether to participate in screening[7,8,9]. This means that screening is not performed routinely. The screening is a complex issue, where future parents are encouraged to make well-informed choices about whether to participate in the screening. Important is the fact that parents should be informed before the US examination about the right not to know, the technical aspects of the screening, and its potential implications[10]. Potential implications include abnormal findings (not specifically cleft lip and palate), and in those cases, if parents wish, the advice to seek further genetic counseling, which may lead to amniocentesis. Thus, informed consent is mandatory before embarking upon this screening process. Midwives, general practitioners, and gynecologists involved in the initial counseling should be trained in counseling practice for this purpose.

Practical Experience With Screening for Cleft Lip and Palate in the Utrecht Regional Unit

The reported reliability of the US in detecting cleft lip and/or palate (CL/P) varies considerably[11]. Several factors may account for the variation, such as the population screened (high risk or low risk), the timing of the US, the experience of the sonographer, the quality of the US equipment, the study design, and the definitions of the outcome parameters. Two studies are important because they were conducted in a nonselected low-risk population, comparable with the Dutch routine screening. Russell et al.[12] studied 10,822 births in the period 1992 to 2002 who had US screening from 18 to 20 weeks of pregnancy. Screening of the face was a standard part of the US performed. The detection ratio for cleft lip with or without cleft palate (CL ± P) was 23% (29/127 babies with CL ± P detected prenatally within a population of 108,220 births in a 10-year period). Isolated cleft palate (CP) without cleft lip and no further congenital abnormalities was not detected on US in this study. The prenatal detection ratio increased with time from 15% (from 1992 to 1996) to 30% (from 1996 to 2002). A study by Offerdal et al.[1] confirms these findings with an overall detection ratio of 45% (34/77) for isolated CL ± P in the low-risk population and a significant increase in the detection

rate from 35% to 58% between the two 9-year periods of the study. It is expected that the detection rate will continue to rise slowly over time due to technical innovations in the equipment and increased experience of sonographers. The specificity of the US for the detection of isolated CL ± P in these studies and other studies is high— almost 100%. The experience at the University Medical Center Utrecht is in line with these studies.

When an orofacial cleft is suspected, pregnant women are referred to a specialized obstetrician in one of the eight designated centers or their satellites for further investigation. This referral system works well. A discussion point is the maximum acceptable time between initial (abnormal) US and the referral to the designated center because parents are kept in uncertainty during this period. Another reason to see the parents without delay is the upper limit to perform termination of pregnancy for a medical reason, which is 24 weeks in the Netherlands. Thus, the time interval to perform karyotyping and other genetic screening frequently is limited. Any wait is undesirable, but in a practical sense often unavoidable, and should be kept to a minimum. The aim is to see the parents in the referral center as soon as possible, and 5 working days is considered the maximum delay.

The images of the first US are stored and made available to the referral center. In all referral centers US screening is repeated using a more extensive protocol[6]. A diagnostic US examination is therefore needed to confirm the provisional diagnosis made at the screening US examination. In the past concerns have been raised about possible detrimental effects of US for the unborn child, but these were not confirmed in recent randomized controlled trials[13]. Current US study protocols[6] adhere to the principle "as low as reasonably achievable (ALARA)"[14], thus sound level/intensity is set as low as possible to allow the optimal image with the minimum US exposure. In normal clinical practice it is extremely improbable to exceed the maximum intensity levels with gray-scale two- dimensional and three-dimensional US. The US exposure needed to detect and confirm a CL ± P is therefore considered as safe.

The current legislation does not yet provide a detailed guideline as to what should happen after confirmation of the diagnosis. The following describes the current practice in our unit in Utrecht with a focus on CL ± P. After confirmation of a cleft lip on US, more detailed assessment is initiated in our unit, implying that the unborn child is

first screened by US by the obstetrician for other defects and a careful family history focused on birth defects is performed.

In Utrecht the consultation of a clinical geneticist is always advised in case any associated abnormalities are detected on US and/or family history suggests syndromal background or increased risk. In such cases karyotyping by amniocentesis is recommended to the parents and usually carried out, provided the results are available before 24 weeks of pregnancy (or in case parents prefer to know anyway). Besides karyotyping other genetic tests are available, and in Utrecht a multiplex ligation-dependent probe amplification (MLPA) test to rule out 22q11.2 deletion syndrome is usually done as well. In case any other structural abnormalities on US and/or chromosomal abnormalities are found, these findings and their possible implications are discussed with the parents by the obstetrician and the geneticist. If the parents opt for voluntary termination of pregnancy, this will take place at the University Hospital instead of an anonymous abortion clinic. This is in line with the recommendations of the legislation and offers the opportunity to perform further examination on the fetus (such as autopsy) and to verify the accuracy of the prenatal diagnosis, which is important for quality control of the system and for the parents regarding the prognosis for possible future pregnancies.

In this context the issue of false-positive findings is relevant. False-positive findings have occurred, but rarely, in the first line during the first US screening in the Utrecht area. These were at all times detected during more extensive follow-up US studies. A third or even a fourth US is made and all other relevant tests are performed to be absolutely sure about the diagnosis of the CL ± P and possible associated congenital anomalies. This is in the stage before significant interventions such as a termination are even considered. In the 20 years of prenatal US screening at the University Medical Centre Utrecht, no cases of misdiagnosis of CL ± P leading to an unintended termination have ever occurred, according to our obstetricians.

In case no other defects are found and the family history is negative too, the parents are offered the option of consultation with a geneticist and/or fetal karyotyping in our regional unit. In these cases parents and counselors should carefully weigh the potential benefits and risks of karyotyping by performing amniocentesis (0.3% spontaneous abortion) against the benefit of more information about the unborn child. The literature mentions quite a significant percentage of associated anomalies

and/or chromosomal abnormalities associated with CL ± P (as a group), with a variance of 24%[15] to 48%[16] for CLP in prenatal studies. A critical appraisal of the studies on associated anomalies, however, shows that the available literature is hampered by a lot of methodological problems, such as inclusion of cases (life birth or all deliveries), variation in follow-up period after birth, variation in the definition of clinical expression of anomalies, variation in technologies available for detection of associated anomalies, patient selection (tertiary centers), differences in population (white or Asian), and prenatal versus postnatal studies. Another problem with the available literature is that in many studies all associated anomalies are lumped together with no discrimination regarding severity. Counseling in this area is certainly not an easy thing to do. Parents may ask us the question: How much chance remains that significant (syndromal) abnormalities are still present unexpectedly after birth in case of a normal advanced US screening (except the cleft), normal karyotyping, and a negative family history? This is an important question, but unfortunately sufficient data are not currently available in the literature for an accurate answer to this seemingly simple question. New studies and better information are urgently needed in this field. In the meantime, we aim to find a balance between informing this group of parents about the risk of associated anomalies and trying to not worry them unnecessarily.

The cleft team is routinely consulted in all cases, except when very severe (lethal) additional anomalies (such as holoprosencephaly or trisomy 13 or 18) are identified, unless the parents choose to continue with the pregnancy regardless of the outcome. The cleft team offers the parents further detailed counseling about the possible consequences of having a CLP. To this purpose the department of gynecology and obstetrics and the cleft team have joined forces and set up a special outpatient clinic. In the outpatient clinic the parents meet a multidisciplinary team, including an obstetrician, the medical psychologist, and a plastic surgeon from our cleft team. During this visit the obstetrician repeats the US in the presence of the plastic surgeon. This allows the plastic surgeon to obtain an ultrasonic three-dimensional view of the cleft. In our experience, this setting improves the quality of the counseling. The etiology and pathogenesis of a CL ± P are explained to the parents and the medical, surgical, clinical, and psychosocial needs of a child with a cleft lip and possible cleft palate are discussed. Explanation is given about the treatment protocol of our cleft unit, and

differences with other cleft teams' protocols are elucidated. Possible operations are described when asked for, and questions and concerns of the parents are addressed. In the Netherlands, home delivery is still performed regularly. In the opinion of our obstetricians there is no major objection against delivery at home of a child with a cleft provided that no other abnormalities are detected prenatally, pregnancy controls are normal, and the mother has normal health. Discussing the risks and benefits of home delivery in the case of a cleft lip frequently forms an important part of the counseling. The potential feeding problems in case of a cleft palate are explained and the measures the parents should take to make feeding as easy as possible, such as buying a Habermann bottle and equipment to express milk from the breast in case the mother prefers to give the baby her own milk. A comprehensive patient information booklet about cleft lip and palate and its treatment, written at our institution, is always provided to the parents. The telephone number of the cleft team coordinator and an e-mail contact address for the cleft team are given to the parents. In many cases there is frequent contact by e-mail between future parents and the medical psychologist of our team about remaining questions and issues during the last trimester of the pregnancy. Although we did not research this specifically, we learned from the feedback of parents that the possibility to keep in contact with the team and/or medical psychologist during the remainder of the pregnancy is appreciated by parents.

A major advantage of this multidisciplinary approach is that pregnant women and health care providers such as the gynecologist, midwife, and nurses are well prepared and know what kind of potential problems to expect at birth. Potential advantages of prenatal cleft diagnosis as formulated by Johnson and Sandy[17]—including psychological preparation, opportunity for parent education, planned neonatal care, and preparation for feeding as well as increased reproductive choices for parents—can be maximally exploited.

Parents tell our medical psychologist that coping with a less-than-perfect child is facilitated by the information they have gathered about the condition before birth. The fact that the cleft team can be contacted at any time gives assurance as well. Our experience supports the statement of Rey-Bellet and Hohlfeld[18] that it is essential for parents to understand that they are not alone in this situation, and this should be a key message in the antenatal counseling process.

Because parents are well informed, it seems that the stress of the parents seeing their child after birth with a cleft is less than the stress of parents in the unexpected cases, which is in accordance with Nusbaum[19]. The study of Kemp et al.[20] suggests that counseling by specialist staff reduces the levels of parental anxiety associated with the diagnosis of a fetal surgical malformation. Our clinical experience seems to be in accordance with these observations, but a prospective study is needed to confirm the positive effect of our counseling policy during the pregnancy. This could be accomplished by studying the coping, stress, uncertainty, and comfort of parents for whom diagnosis was obtained before birth (with counseling) compared with those who were not identified.

With such preparation there is, in general, no need to consult the cleft team instantly after birth, and appointments with the team can be scheduled accordingly.

Choices Made by Dutch Mothers

One of the goals of the Central Organization of the Ministry of Health is to collect all data concerning prenatal US throughout the country by means of an Internet-based registration system, so that the findings of each US performed and its follow-up can be registered directly. In this manner the Central Organization should be able to collect a unique set of data. Unfortunately, the software to analyze this significant data set has not yet been fully developed and consequently, only limited national data are currently available.

The Inspection for Health Care in the Netherlands, however, publishes a detailed report about the number of voluntary terminations of pregnancy in the Netherlands every year, thus affording the opportunity to monitor the possible impact of the new screening policy on the termination rate. In 2007, the latest year for which data are available, the total number of terminations stabilized and the termination number remained stable at 8.6 per 1000 women between 15 and 44 years of age living in the Netherlands, the same as in 2005 and 2006[21]. This is low compared with many other countries but in line with neighboring countries such as Germany and Belgium. There was, however, an increase of 14.4% in the total number of pregnancy terminations performed in the second term of pregnancy (13 weeks), and the number of terminations performed in a hospital (instead of an abortion clinic) between 20 and 24 weeks

increased in comparison to 2005 from 7.4% (140) to 11.5% (270). The trend toward more second-term and hospital terminations (i.e., on medical grounds) started in 2003 and is attributed to the increase in US screening, even before the current legislation was introduced (as more and more women got a prenatal US over the last decade).

Nationwide data about the number of terminations performed specifically in case of CL ± P (as a group) are not currently available. However, the data from the Utrecht region show a very low termination rate for isolated facial clefts (i.e., cases where US and/or other tests have not found any other abnormality). The Utrecht unit covers about 20,000 pregnancies per year. In the 4-year period from 2005 through 2008, a total of 78 cases of cleft lip (and palate) were identified on US prenatally. Of these, 45 were identified as isolated cases of CL ± P, and 33 had associated anomalies on US and/or genetic screening. Three cases of isolated CL ± P and 22 associated cases (mostly trisomy 13 or 18) were terminated by abortion. The regional referral unit at the Erasmus Medical Centre in Rotterdam has recently reported similar numbers[22].

Rozendaal et al.[23] have studied the numbers of the registration of prevalence of CL ±P in the Netherlands by the Dutch Society for Cleft Lip and Craniofacial Abnormalities (DSCLCA) in a recent report on all birth defects in the Netherlands in the period 1997 to 2007 structured by the Minister of HWS[24]. All cleft teams report the type of the cleft of all new babies in a standardized format directly online to the DSCLCA. The number of newborns with a CL ± P varied between a maximum of 395 newborns (2003) and a minimum of 315 newborns (2005) on a population of 16.3 million people and a total of 187,910 live births in 2005. The national average prevalence of CL ± P of the 10-year period 1997 to 2007 was 16.6 per 10,000 life births (11.2 for CL ± P and 5.4 for CP). In the same 10-year period, the registry seems to reveal a slowly declining trend in the prevalence of CL ± P (as a group) in the Netherlands[23]. More detailed analysis of the numbers by Rozendaal et al.[23] suggests a stable prevalence of CP but a decline in CL ± P. The declining trend in the numbers of CL ± P reported by Rozendaal et al.[23] is, however, debatable because numbers are small and the trend may still be within the spread of yearly variation.

The combination of more pregnant women undergoing US screening (even before current legislation was introduced) and increase in second trimester and hospital terminations make it plausible that prenatal screening forms the basis of the

declining prevalence of CL ± P (if indeed true) in the Netherlands. This is in line with international trends[25]. Because termination for isolated CL ± P remains uncommon in the Netherlands, the declining trend in prevalence in the Netherlands is most likely due to termination of pregnancy for multiple congenital anomalies, including CL/P. An alternative explanation brought forward is the Dutch guideline for folic acid supplement[23]. Folic acid supplements are recommended in the Netherlands from 4 weeks before conception to 8 weeks after conception. In the embryo the lip is fused at 7 to 8 weeks after conception, but the palate takes longer (7 to 12 weeks). If we assume that folic acid decreases the chance of CL/P, the current guideline may have a more significant positive effect on the fusion process of the lip compared with the palate, which may account for the lower numbers of babies born with a CL ± P. The beneficial effect of folic acid is, however, still controversial, some studies finding no effect[26]; whereas, other studies suggest that folic acid containing supplements may have a protecting effect[27].

The termination rate for isolated cleft lip (and palate), therefore, remains relatively low and appears to differ from the development in, for example, Israel[28,29]. The explanation for the low termination rate in the Netherlands merits further study, but a good system of prenatal screening, proper counseling of the future parents, sufficient availability of cleft teams to treat the deformity (for 90% of the population, within 1 hour's drive), and health care insurance coverage for cleft lip and palate treatment may all play a role. Jones[30] cited several other factors that possibly influence the voluntary termination of pregnancy rate for CL/P and may help explain the contrast of our Dutch results to those reported by Blumenfeld et al.[28]. First, the group from Haifa is identifying clefts at an earlier time in pregnancy and with transvaginal US as compared with the transabdominal US in the Netherlands at 18 to 22 weeks. In the Netherlands most women have, therefore, experienced significant fetal movement by the time they are making their choice. Second, there may be a fundamental difference in the "perception of burden" of clefting and other congenital abnormalities between the Dutch and Israeli populations. Cultural, religious, and socioeconomic factors are well-known influences on parental willingness to accept the birth of a "less than perfect" child[30].

Future Implications

An important issue is uniformity in counseling of parents after detecting a suspected orofacial cleft on US. In this article we describe our experience in Utrecht, but a questionnaire sent to all Dutch cleft teams in 2007 showed significant local differences in prenatal counseling practice between cleft teams, a few cleft teams not being involved at all. Now that the government has outlined a uniform system of general prenatal screening in the Netherlands, it seems relevant to develop a uniform counseling process for the regional centers in case a CL ± P is detected on US. To achieve this goal it is desirable that specialists from the local cleft teams learn to work closely together with the people involved in the screening process to achieve the required high-quality care in this complex field. To provide a solid basis for this cooperative care, the Dutch Society of Plastic and Reconstructive Surgery initiated the development of a national multidisciplinary evidence-based guideline for prenatal counseling of pregnant women carrying a child with possible a CL ± P in 2008. All parties involved in cleft care will be represented. Both parents and individuals with CL ± P will participate in the development of this guideline, as well as parents who have already undergone the process of prenatal screening and counseling, because they have experienced the potential drawbacks of prenatal screening such as emotional disruption of the pregnancy and the inability to correct the problem prenatally[31]. The guideline is not only aimed at improving the quality of the information provided to the parents but also optimizing the way they are informed because parents perceive the manner in which they receive the diagnosis as important[19]. Based on a combination of factors (technical innovations in genetic diagnostic tools, increasing knowledge about the genetic background of syndromes related to CL ± P, and the demand of [some] parents to be maximally informed about the genetics of their child), we foresee an increasingly important role of the clinical geneticist in the counseling process itself and therefore in the guideline being developed. It will be of interest to monitor the impact of the new regulation and the counseling on the overall pregnancy termination rate for CL ± P in Netherlands in years to come.

CONCLUSION

In the Netherlands a new nationwide routine screening system for congenital birth defects was introduced in 2007. The main aim of this system is the detection of Down syndrome and neural tube defects. Additionally, screening for CL ± P is also performed. The screening is offered to all pregnant women, who are free to participate or not. The system is regulated by a central organization for prenatal screening and covered by the health insurances. As a consequence more children with a cleft are diagnosed prenatally. In response to this, the existing cleft teams in the Netherlands are setting up specialized prenatal cleft clinics to participate in the counseling of pregnant women carrying a child with a possible CL ± P. The termination of pregnancy rate for isolated CL ± P remains low. A national evidence-based guideline for prenatal counseling for CL ± P is currently in preparation. The primary goal is to provide complete, independent, unbiased, and uniform information about CL ± P to parents in the prenatal period. The secondary aim of this guideline is to accomplish uniformity in the counseling process in the eight designated Dutch referral centers for prenatal screening and their associated cleft teams in case a CL ± P is diagnosed prenatally.

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Diagnostic accuracy of transabdominal ultrasound in detecting prenatal cleft lip and palate: a systematic review

Ultrasound Obstet Gynecol 2010; 35: 495–502

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ABSTRACT

Objectives To systematically review the diagnostic accuracy of second-trimester transabdominal ultrasound in detecting orofacial clefts in low- and high-risk populations and to compare two-dimensional (2D) with three-dimensional (3D) ultrasound techniques.

Methods MEDLINE and EMBASE were searched for articles published in English, Dutch, French or German using the keywords 'cleft' and 'ultrasound' or 'screening' or 'sonogram' and 'prenatal' or 'antenatal' or 'fetus' to identify cohort studies and randomized trials in order to assess the detection rate by prenatal ultrasound of cleft lip and palate in high-risk and low-risk pregnant women.

Results Of 451 citations identified, 27 met the criteria for the systematic review, 21 involving unselected low- risk populations and six involving high-risk populations. In the selected studies there was diversity in the gestational age at which the ultrasound examination was performed and there was considerable variety in the diagnostic accuracy of 2D ultrasound in the low-risk women, with prenatal detection rates ranging from 9% to 100% for cleft lip with or without cleft palate, 0% to 22% for cleft palate only and 0% to 73% for all types of cleft. 3D ultrasound in high-risk women resulted in a detection rate of 100% for cleft lip, 86% to 90% for cleft lip with palate and 0% to 89% for cleft palate only.

Conclusions 2D ultrasound screening for cleft lip and palate in a low-risk population has a relatively low detection rate but is associated with few false-positive results. 3D ultrasound can achieve a reliable diagnosis, but not of cleft palate only.

INTRODUCTION

In The Netherlands, transabdominal ultrasound screening at 20 weeks of pregnancy was made universally accessible by legislation and health insurance coverage in 2007. On average, more than 95% of Dutch pregnant women make use of ultrasound screening. This usually involves two-dimensional (2D) ultrasound, and is performed in a primary care setting by certified midwives, sonologists and obstetricians. If there is suspicion of a fetal anomaly, the pregnant woman is referred to a certified tertiary care center for detailed ultrasound imaging, counseling and other diagnostic procedures as indicated. During this detailed screening, special attention is paid to the fetal upper lip[1], and orofacial-cleft teams have found themselves confronted with prenatal cleft cases more frequently since the introduction of routine ultrasound screening[2].

Cleft lip with or without cleft palate is amongst the most common congenital facial malformations in The Netherlands, with a combined incidence of 1.8 per 1000 births per year[3]. Fetuses with orofacial clefts identified by ultrasound, however, represent a different group from cleft neonates since a considerable number of cases never reach term due to potentially lethal associated malformations leading to termination of pregnancy[4].

In 1981, Christ and Meininger[5] were the first to report the detection of a cleft lip and palate deformity by ultrasound. Nyberg et al.[6] developed an ultrasound classification system based on morphological criteria. A large number of studies reporting on the accuracy of prenatal ultrasound in detecting fetal clefts have been published, but to the best of our knowledge there have been no systematic reviews focusing on the prenatal detection rates of cleft lip and palate by ultrasound. We therefore conducted a systematic review of the literature to identify all representative studies reporting on the accuracy of prenatal transabdominal sonographic detection of cleft lip and palate during the second trimester (14 – 28 weeks) of pregnancy.

METHODS

In November 2008 we performed a systematic literature search of the MEDLINE and EMBASE databases as detailed in Figure 1. The detected citations from several databases were combined and duplicate articles were excluded. The titles and abstracts of all selected publications were inspected for relevance based on the following inclusion criteria:

- population: pregnant women in their second trimester (14 – 28 weeks' gestation) of pregnancy;
- index test: transabdominal ultrasound examination;
- reference standard: confirmation of diagnosis of cleft lip or palate by postnatal findings or pathology report;
- outcome: cleft lip only (CL), cleft lip with or without cleft palate (CL ± P) or cleft palate without cleft lip (cleft palate only; CP).

Additional inclusion criteria were:

- publication in or after 1990;
- retrospective and prospective cohort study or clinical trial;
- more than 1000 women if population-based study;
- use of state-of-the-art equipment if study included high- risk pregnant women;
- publication language restricted to English, French, German or Dutch.

Initial exclusion based on title and abstract was carried out independently by two reviewers (W.M. and T.B.). The quality of the studies was assessed through evaluation of the internal and external validity, as described by Bossuyt et al.[7], including: (1) availability and validity of the sonographic and neonatal outcome as well as sufficient description of index and reference standards; (2) whether, in population-based studies, ultrasound examination was performed with the operator unaware of the pregnant woman's risk of having a fetus with a cleft; (3) whether evaluation of neonatal outcome was performed without knowledge of the ultrasound results (verification).

RESULTS

The literature search yielded 451 citations. There was no disagreement between the two assessors regarding inclusion of studies. The initial screening by title identified 66 abstracts that were potentially relevant. In total 27 studies met all the inclusion criteria as well as the internal and external validity criteria (Figure 1). Two different ways of patient selection were distinguished: 21 studies consisted of unselected population-based groups of pregnant women ('low-risk population study') and six studies dealt with a population with a positive family history and/or prescreened fetuses who were suspected to have CL ± P. Members of these populations had already passed the primary care stage, were clinically suspected or confirmed as having a CL ± P fetus and had been referred for further evaluation ('high-risk population study'). Variability in the design and results of the selected studies is summarized in Tables 1 and 2 and Tables S1 and S2 online. There was no literature found on the prenatal diagnosis of median clefts.

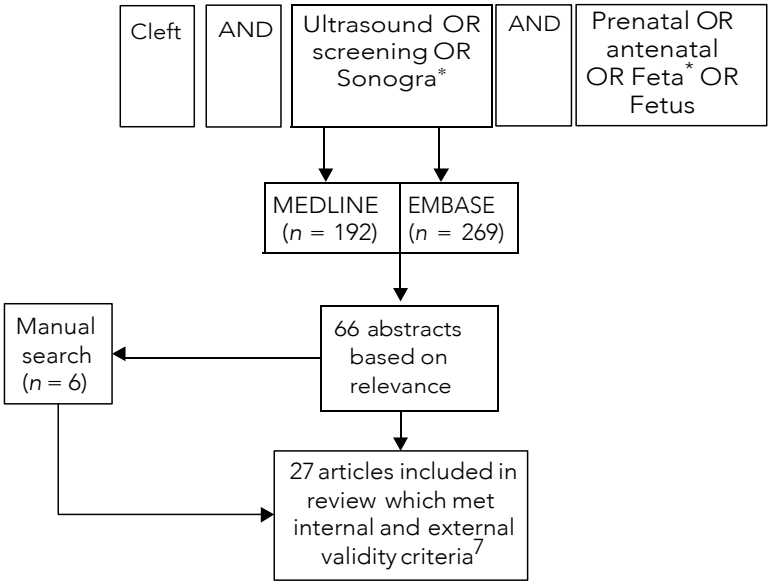

Figure 1 *Search string and flow of selection process of retrieved citations.*

Table 1 *Summary of studies reporting detection rate for cleft lip and palate of two-dimensional ultrasound screening in low-risk populations*

			Detection rate (n (%))		
Reference	n	*GA (weeks)*	*All types of cleft*	*Cleft lip with or without cleft palate (CL ± P)*	*Cleft palate only (CP)*
Retrospective studies					
Chitty[10] (1991)	8432	< 24 (95%)	2/9 (22)	2/6 (33)	0/2 (0)
Shirley[12] (1992)	6183	< 22	3/9 (33)	3/7 (43)	0/2 (0)
Roberts[11] (1993)	12 909	16 –24	0/4 (0)	NS (NS)	NS (NS)
Stoll[14] (2000)	265 679	23.1 (13 –39); 28.3 (20 –38)*	47/177 (27); 19/121 (16)*	NS (NS)	NS (NS)
Shaikh[8] (2001)	250 000	NS	23/270 (9)	NS (NS)	0/140 (0)
Sohan[13] (2001)	35 880	18 –20	14/20 (70)	14/28 (50)	0/8 (0)
Cash[9] (2001)	23 577	18 –20	17/26 (65)	15/17 (88)	2/9 (22)
Prospective studies					
Levi[20] (1995)	16 610	≥ 23	5/24 (21)	NS (NS)	NS (NS)
Anderson[28] (1995)	7880	16 –20	NS (NS)	1/4 (25)	0/1 (0)
Hafner[19] (1997)	5407	17 and 22	5/8 (63)	2/5 (40)	NS (NS)
Forrester[17] (1998)	200 000	NS	32/376 (9)	32/235 (14)	0/141 (0)
Boyd[15] (1998)	33 376	18 –22	NS (NS)	12/25 (48)	NS (NS)
Grandjean[18] (1999)	NS	28 ± 7.4	57/316 (18); 18/316 (6)†	56/144 (39)	1/72 (1)
Stefos[25] (1999)	7236	18 –22	NS (NS)	3/6 CL only (50)	NS (NS)
Clementi[16] (2000)	709 030	25.5 (15 –38)‡	161/751 (21)	148/553 (27)	13/198 (7)
Robinson[23] (2001)	154 793	25.5 (23.2 –27.9)	41/56 (73)	NS (NS)	NS (NS)
Wayne[27] (2002)	17 551	20 –22	NS (NS)	9/12 (75)	NS (NS)
Tonni[26] (2005)	1856	21 ± 2	NS (NS)	2/2 (100)	NS (NS)
Nikkila¨ [21] (2006)	141 240	< 23 (49%)	NS (NS)	21/240 CL only (9)	NS (NS)
Russell[24] (2008)	108 220	28.3 ± 6.0	29/225 (13)	29/127 (23)	0/98 (0)
Offerdal[22] (2008)	49 314	19 ± 2	35/101 (35)	14/41 (34) (in 1987 –1995); 21/36 (58) (in 1996 –2004)	0/24 (0)

Note: this table is available online as Table S1, with additional information on study populations and inclusion and exclusion criteria. Only the first author's name of each study is given. *Cases of isolated cleft lip and palate. †Before 24 weeks. ‡For isolated cleft cases only. GA, gestational age; NS, not stated.

Table 2 *Summary of studies reporting detection rate for cleft lip and palate of ultrasound screening in high-risk populations*

			Detection rate (n (%))			
Reference	n	*GA (weeks)*	*All types of cleft*	*Cleft lip with or without cleft palate (CL ± P)*	*Cleft lip with cleft palate (CL + P)*	*Cleft palate only (CP)*
Retrospective studies						
Chen[29] (2001)	21	20 –34 (mean, 25.3)	NS (NS) 3D/Uni: 16/16 (100)	2D/Uni: 5/16 (31) 2D/Bi: 1/5 (20) 3D/Bi: 5/5 (100)	NS (NS)	NS (NS)
Rotten[31] (2004)*	96	22 –39 (mean ± SD, 28.2 ± 4.1)	NS (NS)	2D/Uni: 27/31 (87) 2D/Bi: 2/3 (66)	2D/Uni: 37/42 (88) 2D/Bi: 18/20 (90)	NS (NS)
Hanikeri[30] (2006)	216	15 –20 (80.5%)	2D/Uni: 39/96 (41) 2D/Bi: 8/18 (44)	NS (NS)	NS (NS)	0/95 (0)
Prospective studies						
Johnson[33] (2000)*	31	15 –35 (mean ± SD, 24.8 ± 5.0)	NS (NS)	2D: 26/28 (93) 3D: 28/28 (100)	2D: 9/22 (41) 3D: 19/22 (86)	NS (NS)
Chmait[32] (2002)*	57	15 –35 (mean ± SD, 24.6 ± 5.2)	NS (NS)	2D: 41/45 (91) 3D: 45/45 (100)	2D: 19/41 (46) 3D: 37/41 (90)	NS (NS)
Wang[34] (2007)	30	16 –36 (mean, 26)	NS (NS)	2D: 21/22 (96) 3D: 22/22 (100)	NS (NS)	2D: 2/9 (22) 3D: 8/9 (89)

Note: this table is available online as Table S2, with additional information on study populations and inclusion and exclusion criteria. Only the first author's name of each study is given. *The reported CL ± P cases for Rotten and Levaillant[31] , Johnson *et al.*[33] and Chmait *et al.*[32] were CL only. Bi, bilateral; GA, gestational age; NS, not stated; Uni, unilateral.

Low-risk populations

Of 21 low-risk population studies (Table 1), all were cohort studies, seven[8–14] being retrospective and 14[15–28] being prospective. The retrospective cohort studies reported a large variety in the diagnostic accuracy of 2D ultrasound, with detection rates ranging from 0%[11] to 70%[13] for prenatal detection of all types of cleft, 33%[10] to 88%[9] for prenatal detection of CL ± P and 0%[8,10,12,13] to 22%[9] for detection of CP. In prospective cohort studies, detection ranged from 9%[17] to 73%[23] for prenatal detection of all types of cleft, 9%[21] to 100%[26] for prenatal detection of CL ± P and 0%[17,22,24,28] to 7%[16] for detection of CP. In several studies, all prenatal diagnosis of CL ± P was confirmed following delivery or postmortem, indicating no false- positive diagnoses[9,10,13,15,18,19,23,26,27] or high specificity when there was complete follow-up of all negative ultrasound diagnosis[21,22,24].

The two most recent prospective cohort studies[22,24] evaluated a large study population to assess the accuracy of detecting facial clefts in a low-risk population. Russell et al.[24] assessed 108 220 births in the period from 1997 to 2002, during which prenatal ultrasound at 18 to 20 weeks was available to all pregnant women (2D imaging of the fetal lip was a standard component of the prenatal sonographic scan). During this study period, 127 cleft babies were born, of which 29 had CL ± P predicted prenatally, resulting in a detection rate of 23%. None of the 98 cases of CP was diagnosed prenatally. The prenatal detection rate of orofacial clefts increased significantly over time (14% in 1992 – 1996 and 30% in 1996 – 2002, P = 0.03). The other recent prospective cohort study, by Offerdal et al.[22], also showed a significant increase in prenatal detection with time (34% in 1987 – 1996 and 58% in 1996 – 2004, P = 0.03). This study included 49 314 pregnancies representing a non-selected population. Ultrasound visualization of the fetal face was part of the routine examination. CL ± P was detected prenatally in 35 of the 77 (45%). Of these 35 CL ± P cases, 24 (69%) were detected during routine second-trimester ultrasound exam. Not one of the 24 cases of CP was diagnosed prenatally.

High-risk populations

Of the six selected high-risk population studies[29–34] (Table 2), three were retrospective[29–31] and three were prospective[32 – 34]. Several ultrasound methods were described; however, in most cases multiplanar views were used, which allowed a simultaneous analysis in sagittal, axial and coronal planes. In their retrospective study, Hanikeri et al.[30]

found a detection rate of 41% (39/96) for unilateral clefts and 44% (8/18) for bilateral cases. All 3D ultrasound studies showed a detection rate of 100% with the exception of the study of Rotten et al.31 who reported a detection rate of 87% (27/31) for unilateral clefts and 66% (2/3) for bilateral clefts. Three studies assessed the detection rate of CL + P, finding rates of 88% (37/42) in unilateral CL + P[31], 90% (18/20) in bilateral CL + P[31] and 90% (37/41)[32] and 86% (19/22) of all CL + P on 3D imaging[33]. Two studies assessed the detection rate for CP, which varied from 0% (0/95) on two-dimensional imaging[30] to 89% (8/9) on three-dimensional (3D) imaging[34]. The study of Chen et al.[29] as well as that of Wang et al.[34] showed a significant increase in the detection rate of 3D ultrasound in comparison with 2D ultrasound ($P < 0.05$).

DISCUSSION

This review confirms that studies reporting on the accuracy of 2D ultrasound in detecting CL ± P in low- risk populations demonstrate a wide variety in diagnostic accuracy. Most studies reported detection rates between 9% and 50%, indicating a considerable number of missed diagnoses of CL ± P. Moreover, the overall reported rate of false-positive diagnosis for prenatal CL ± P in routine screening was low. In high-risk populations, detection rates of CL ± P using 3D ultrasound in tertiary care centers were mostly between 60% and 100%, with the exception of CP only.

In general, the methodology was of poor quality and inconsistent. As a consequence, comparison was hardly possible (Table 3). Studies published before 1990 were excluded since ultrasound technology in those days is incomparable with current techniques. Moreover, studies involving low-risk populations should have included more than 1000 women, because of the low incidence of orofacial clefts, but there was considerable difference in the size of these study populations. Those that included small populations consequently reported higher sensitivities[26]. For example, Tonni et al.[26] reported a detection rate of 100%, but only two cases of orofacial cleft were diagnosed. None of the studies performed a preliminary sample size power calculation. Studies that included high-risk referred women should have used 3D ultrasound, because this has been shown to enhance significantly the 2D examination[34,35] and is currently used in tertiary care centers, yet not all of them did.

Table 3 *Sources of variability in detection rates of orofacial clefts with prenatal ultrasound screening, and suggestions for further research*

Sources of variability	*Suggestions for improvement of diagnostic accuracy*
Gestational age at scan	Enroll pregnant women prospectively with a standard protocol in which ultrasound screening takes place
Inclusion/exclusion criteria	Enroll low-risk pregnant women consecutively to ensure they all have the same *a priori* risk; prevent spectrum bias (e.g. all from one region)
Index test	Enroll pregnant women prospectively so whole study population receives an ultrasound evaluation
Case definition	Ensure inclusion of all cases of orofacial cleft: CL, CL ± P and CP, both isolated and those with other anomalies; divide results into these different groups
Screening method	Ensure screening of fetal face is standard in ultrasound protocol
Ultrasound technology and experience of sonologist	Evaluate fetus with same ultrasound technique and if cleft is suspected, analyze face in three orthogonal planes and with 3D ultrasound. Ensure same level of ultrasound performance and level of expertise of sonologist
Sample size	Evaluate stability of estimated prevalence rate of orofacial cleft in light of expected sensitivity and specificity
True population differences	Describe general cleft incidence, because of variation between different populations
Loss to follow-up	Ensure complete follow-up of whole study population for designing valid two-by-two table so sensitivity and specificity can be properly analyzed
Reference standard	Specialist evaluation to confirm orofacial cleft after birth; evaluation of dysmorphic features by clinical geneticist and possible laboratory evaluations might be needed; name postnatal time frame when anomalies were evaluated

3D, three-dimensional; CL, cleft lip; CP, cleft palate; CL ± P, cleft lip with or without cleft palate.

There was a substantial amount of potential bias in the majority of included studies. Many were designed retrospectively, which increases the risk of bias. Furthermore, the mean gestational age at which the routine ultrasound examination was performed differed significantly (Tables 1 and 2), the average being 24 weeks. This would therefore have led to differences in detection rates, because there is a significant difference in the ability to diagnose facial clefts before 20 weeks compared with later in pregnancy[36].

Furthermore, recruitment of the study population was not properly designed in most studies. A population-based study should contain a cohort of unselected, consecutive pregnant women to ensure that they all have the same a priori risk of having a child with an orofacial cleft. The study of Boyd et al.[15], for example, identified all fetuses and babies of women booked for delivery with a certain ZIP code. In this way, high-risk pregnancies referred from outside the region were automatically excluded. In most studies, however, pregnant women who were already suspected of carrying a fetus with CL ± P were included, implying a spectrum bias which could have resulted in an artificially high detection rate. Another potential source of bias was the way in which the study populations were selected. Most authors described a cohort of all deliveries and in some cases the stillbirths and intrauterine deaths in a certain period of time and compared these with all registered malformations. They assumed that all included women had undergone routine ultrasound examination during their pregnancy, but could not verify this. As a consequence, the number having undergone ultrasound, i.e. the study population, was over-reported, leading to an invalid detection rate. Moreover, it can be assumed that there was ascertainment bias as well, meaning that the reported postnatal risk of facial cleft was under-reported in some studies[10,14,16,28], because there are probably cases of cleft palate missed postnatally that are not presented in their results.

Overall, CP only, i.e. without the presence of CL, was hardly ever detected in the primary care setting. In several studies this was incorrectly assumed to be a legitimate reason for excluding these cases in advance[8,23,37]. The only report of a strikingly high detection rate was the recent study of Wang et al.[34], who used a combined approach of 2D and 3D ultrasound in both orthogonal display and multi-slice-view ™ modes. Obviously, excluding cases of CP only gives a higher detection rate of orofacial clefts when compared with prenatal recognition calculations in which CP only is included. Examining the results of Clementi et al.[16], when CP only is included in the calculations, the prenatal detection rate of clefts decreases from 148/553 (27%) to 161/751 (21%). There was a discrepancy in the way ultrasound screening was performed. In tertiary referral centers the operator expertise is greater, which will result in increased detection rates of orofacial clefts[38,39]: Ecker and Frigoletto[39] documented that sensitivity of ultrasound screening depends on the operator, while Crane et al.[38] in their

randomized control trial of prenatal ultrasound screening found a significantly higher rate of anomaly detection in a tertiary versus a non-tertiary center. Additionally, some studies reported the detection rate of a variety of malformations, CL ± P being just one of many[10 – 12,15,17,28]. Although these studies were based on a standard evaluation of the fetal face, screening for orofacial clefts was not the main goal of the study. Routine fetal anatomical survey will increase detection of CL ± P, as shown by Robinson et al.[23] who reported a detection rate of 0.73 but only included women who had adequate visualization of the fetal face. Differences in examination protocol could explain the lower detection rate in a low-risk population. Some ultrasound protocols completely ignore the face, some use selected views and only some include a comprehensive examination of the fetal face[40]. Routine visualization of the fetal face and training of sonologists in the primary care setting seems to be one of the keys for successful detection. It is not, however, only operator expertise but also the ultrasound technique that has an impact on detection rates. Babcook et al.[41] performed comprehensive studies analyzing the fetal face in three orthogonal planes. Facial anomalies were found in 20 – 30% of cases when only one or two planes were used, while detection rates rose to nearly 90% when all three planes (coronal, axial and sagittal) were analyzed. Improvement in expertise and better techniques have already led to an improvement in detection rates, as shown in the studies of Russell et al.[24] and Offerdal et al.[22].

Another reason for variability in detection rates was the different definition of outcome. Some studies assessed the detection rate of CL ± P, not distinguishing between isolated clefts and clefts with associated anomalies. Stoll et al.[14] believed that children with clefts should be divided into two groups, an 'isolated' group when only CL ± P is present and an 'associated' group when additional malformations are present, illustrating this theory by the dissimilar detection rates of isolated CL ± P (2.3%) and CL ± P with multiple malformations (64.3%). Offerdal et al.[22] reported a detection rate for CL ± P associated with other anomalies of 63% compared with 53% for isolated CL ± P. Hafner et al.[19] showed 100% detection of facial malformations in the presence of associated anomalies. Clementi et al.[16] demonstrated that the overall detection rate for orofacial cleft was 26.8%, this rate increasing from 17.8% (65/366) for isolated orofacial cleft to 44.4% (83/187) for orofacial cleft with associated anomalies. Similarly, they reported an increasing detection rate of CP without CL of 0.9% (1/109) when

the cleft was isolated to 13.5% (12/89) when it was associated with other anomalies. In short, an additional anomaly is usually more evident and detection of one might prompt more detailed and targeted screening, leading to a higher chance of detecting an orofacial cleft.

However, all of these potential sources of bias could not wholly explain the large variability in detection of orofacial clefts. Diagnostic accuracy in evidence-based medicine is assessed not by detection rate, but by sensitivity and specificity. Sensitivity is the probability that an abnormality present in the fetus is actually detected by ultrasound when postnatal outcome confirms an abnormality, and specificity is the probability that the outcome of the ultrasound examination is normal when postnatal outcome confirms there is no abnormality. Hence, complete follow-up, including the false-positive and false-negative diagnoses of all fetuses enrolled prospectively in the study, is essential. Moreover, a sample size calculation should be performed to design an accurate diagnostic study[42]. Finally, to ensure valid interpretation of the results, studies need to be designed prospectively, enrolling consecutive pregnant women who are screened routinely, prior to suspicion of a cleft.

Despite the fact that receiving a prenatal diagnosis of facial cleft can be distressing to parents, it gives them the possibility to prepare themselves in an emotional and practical way[43]. Health professionals are expected to have accurate and clear answers on possible questions posed by the parents following ultrasound diagnosis[44]. Furthermore, it is important to differentiate correctly between the various types of orofacial cleft, because this affects fetal prognosis[6]. Different types of cleft may be variously associated with severe additional anomalies[4], generally resulting in poor outcome, while isolated clefts have low mortality and morbidity rates and are primarily a functional and esthetic problem. It is therefore important to distinguish between isolated clefts and those with associated anomalies. Furthermore, many syndromes have clefting as part of their phenotype and a cleft may be the only sign of a potential serious aneuploidy, such as trisomy 18[4], while CL only is associated with a very small percentage of chromosomal anomalies[45]. Because an ultrasound examination can never rule out a chromosomal aberration, patients should receive genetic counseling and should be offered karyotypic analysis of their fetus[44], although there are no set guidelines regarding to which patients this analysis should be offered. Further research should delineate the specific indications.

Transvaginal ultrasound was not considered in this review, although high detection rates have been reported by Bronshtein et al.[46]. Unfortunately, theirs is the only study to analyze data on transvaginal ultrasound in the detection of clefts. This would be a good option for screening; it can be performed during early pregnancy and is technically less difficult in comparison to 3D ultrasound. However, transvaginal ultrasound is a more invasive method, which does not fit the principles of a good screening test, as formulated in 1968 by Wilson and Jungner of the WHO[47]. In the Netherlands, however, routine screening is not possible using 3D ultrasound and is instead performed using 2D ultrasound. From our independent analysis of 3D studies, it appears that 3D ultrasound can achieve a reliable diagnosis, yet these studies all took place in high-risk centers with greater expertise. Moreover, there is the possibility of confounding factors such as examination time, which, although not specifically mentioned in this review, one would assume to be longer for 3D than for 2D ultrasound. At present, it is questionable whether 3D ultrasound is practicable as a screening tool. A screening test should be feasible for use in the population (all pregnant women) and the benefit of case detection should be economically balanced. Orofacial cleft is not a common anomaly. The difference in accuracy between 2D and 3D ultrasound is not yet balanced by the increased costs, duration of examination, expertise and facilities necessary for acceptance of 3D ultrasound as a screening test. It is, however, important to refer the patient if an orofacial cleft is suspected. 3D ultrasound can diagnose CP and associated anomalies more accurately than can 2D ultrasound. Moreover, doctors who perform ultrasound in tertiary centers are more specialized, have more experience and, above all, have more time.

In conclusion, based on this review, transabdominal 2D ultrasound screening for orofacial clefts in a low-risk population has a relatively low detection rate but low false-positive diagnosis, with a significant improvement in detection rate over time. To continue this progress, ultrasound screening should routinely include detailed examination for orofacial clefts. Additionally, further improvements in the expertise of sonologists and advances in ultrasound technology should result in the continued improvement in detection accuracy and rates. Because of the relatively low detection rates at present, parents need to be aware that a negative ultrasound result does not necessarily mean that their unborn child is without orofacial cleft. While 3D ultrasound

can achieve a reliable diagnosis of fetal CL ± P, this does not rule out cases of CP only. It is therefore important to refer pregnant women to a tertiary care center when an orofacial cleft is suspected in the primary care setting. Finally, 3D ultrasound can provide a more precise image of the defect, allowing parents to produce realistic expectations.

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Table S1 *Summary of studies reporting detection rate for cleft lip and palate of two-dimensional ultrasound screening in low-risk populations*

Reference	*Population*	n	*Inclusion criteria*	*Exclusion criteria*	*GA (weeks)*	*All types of cleft*		*Cleft lip with or without cleft palate (CL ± P)*		*Cleft palate only (CP)*	
						n	%	n	%	n	%
Retrospective studies											
Chitty[10] (1991)	London, UK: all fetuses examined by US (pregnancies and TOPs) in Luton and Dunstable Hospital (1988–1989)	8432	Booked for delivery > 24 weeks; if examination incomplete or abnormality detected, second or further scans performed	NS	< 24 (95%)	2/9	22	2/6	33	0/2	0
Shirley[12] (1992)	Middlesex, UK: all fetuses examined by US (all pregnancies and TOPs) in Hillingdon Hospital (1989–1990)	6183	Booked for delivery in that hospital; ultrasound in gestational week 19	Fetal facial profile only examined to detect severe bilateral facial clefting	< 22	3/9	33	3/7	43	0/2	0
Roberts[11] (1993)	Auckland, NZ: all babies born in National Women's Hospital (1988–1989)	12909	All deliveries including referrals and fetuses	Deliveries in hospitals outside Auckland	16–24	0/4	0	NS	NS	NS	NS
Stoll[14] (2000)	Strasbourg, France: consecutive deliveries and fetus of 11 hospitals (1989–1998), and children born with orofacial cleft	265679	All deliveries including referrals and fetuses	Cases of cleft palate without cleft lip	23.1 (13–39); 28.3 (20–38)*	47/177; 19/121*	27; 16*	NS	NS	NS	NS
Shaikh[8] (2001)	Bristol, UK: all children born with cleft lip and/or palate (1991–1998) in Frenchay and St Michael's Hospital catchment area with approximately 250 000 live births	250000	Pregnant women in catchment area	Cases of cleft palate without cleft lip (n = 140); pregnancies ending in TOP (n = 2)	NS	23/270	9	NS	NS	0/140	0
Sohan[13] (2001)	Bristol, UK: all deliveries in obstetric database Stork, EDS, Bristol, UK (1991–1999)	35880	All deliveries including referrals and all pre- and postnatal cases of isolated cleft (seen in 8-year period)	Women who did not undergo an 18–20-week ultrasound exam	18–20	14/20	70	14/28	50	0/8	0
Cash[9] (2001)	Cambridge, UK: consecutive pregnant women undergoing routine screening in Rosie Maternity Hospital (1993–1997)	23577	All pregnant women including referrals	2 cases with associated anomalies; 2 cases of intrauterine death	18–20	17/26	65	15/17	88	2/9	22
Prospective studies											
Levi[20] (1995)	Belgian University Hospital: pregnant women at low risk for congenital anomalies attending antenatal clinic	16610	Had at least one ultrasound exam	High-risk pregnancies	≥ 23	5/24	21	NS	NS	NS	NS
Anderson[28] (1995)	Christchurch, NZ: reports of sonographic studies (1991–1993)	7880	All sonograms performed between 16 and 20 weeks	Cases with no follow-up data (n = 23)	16–20	NS	NS	1/4	25	0/1	0
Hafner[19] (1997)	Vienna, Austria: pregnant women who signed up for delivery (1992–1995)	5407	All women who underwent ultrasonography during gestational week 22	Patients delivering in a hospital outside Vienna	17 and 22	5/8	6 3	2/5	40	NS	NS

Forrester[17] (1998)	Hawaii, USA; all population-based registry of malformations (HBDP) (1987–1996)	c. 200000	Pregnancies ending in Hawaii, regardless of outcome	Cases with no follow-up data	NS	32/376	9	32/235	14	0/141	0
Boyd[15] (1998)	Oxford, UK: registration of all congenital malformations of livebirths, still births and intrauterine deaths (1991–1997)	33376	All pregnant women with zip code starting OX	All referrals from outside Oxford region; cases of cleft palate without cleft lip	18–22	NS	NS	12/25	48	NS	NS
Grandjean[18] (1999)	Multicenter Eurofetus Study: registration of all congenital malformations in 14 European countries (1990–1993)	NS	NS	Referral for suspected malformation	28 ± 7.4	57/316; 18/316†	18; 6†	56/144	39	1/72	1
Stefos[25] (1999)	Ioannina, Greece: pregnant women with and without independent risk factors, delivering in Ioanna University Hospital	7236	High- and low-risk populations (including referrals)	NS	18–22	NS	NS	3/6 CL only	50	NS	NS
Clementi[16] (2000)	EUROSCAN Study: 12 European countries; all live births, stillbirths and intrauterine deaths registered in a database (1996-1998)	709030	Including referrals; ultrasound claimed to be routine except for in The Netherlands and Denmark	NS	25.5 (15–38)‡	161/751	21	148/553	27	13/198	7
Robinson[23] (2001)	Boston, USA: all women who gave birth in Brigham and Women's Hospital (1990–2000)	154793	NS	Cases of cleft palate without cleft lip; ultrasound exam performed for indications other than anatomical survey	25.5 (23.2–27.9)	41/56	73	NS	NS	NS	NS
Wayne[27] (2002)	London, UK: all pregnant women undergoing prenatal ultrasound in St. George's Hospital; registration in database (1996–2000)	17551	Including referrals	Cases with associated malformations or abnormal karyotype	20–22	NS	NS	9/12	75	NS	NS
Tonni[26] (2005)	Italy: cohort of all pregnancies in 2003	1856	All low-risk pregnancies	NS	21 ± 2	NS	NS	2/2	100	NS	NS
Nikkilä[21] (2006)	Malmöhus, Denmark: prenatal diagnosis of all newborns and aborted fetuses (1984–1999)	141240	Women who were residents of Malmöhus (based on municipal codes)	NS	< 23 (49%)	NS	NS	21/240 CL only	9	NS	NS
Russell[24] (2008)	Nova Scotia, Canada: three databases with all births in that region plus data from The Cleft Palate Database in same region (1997–2002)	108220	All cases of facial cleft, including abortions	Cases of cleft palate without cleft lip	28.3 ±6.0	29/225	13	29/127	23	0/98	0
Offerdal[22] (2008)	Trondheim, Norway: all consecutive livebirths, stillbirths and intrauterine deaths, divided into two periods (1987–1995 and 1996–2004)	49314	Non-selected population of pregnant women undergoing prenatal ultrasound	Referrals of suspected cases outside area of center; cases of cleft palate without cleft lip	19 ± 2	35/101	35	14/41 (in 1987–1995); 21/36 (in 1996–2004)	34; 58	0/24	0

Only the first author's name of each study is given. *Cases of isolated cleft lip and palate. †Before 24 weeks. ‡For isolated cleft cases only. GA, gestational age; NS, not stated; NZ, New Zealand; TOP, termination of pregnancy; UK, United Kingdom; US, ultrasound.

Table S2 *Summary of studies reporting detection rate for cleft lip and palate of ultrasound screening in high-risk populations*

Reference	*Population*	n	*GA (weeks)*	*Inclusion criteria*	*Exclusion criteria*	*All types of cleft*		*Cleft lip with or without cleft palate (CL ± P)*		*Cleft lip with cleft palate (CL+P)*		*Cleft palate only (CP)*	
						n	%	n	%	n	%	n	%
Retrospective studies													
Chen[29] (2001)	All data of cleft cases detected by US (1996–2000), Cheng Kung University Hospital, Taiwan	21	20–34 (mean, 25.3)	Fetuses with facial cleft	None stated	NS	NS	2D/Uni: 5/16 2D/Bi: 1/5 3D/Uni: 16/16 3D/Bi: 5/5	2D/Uni:.31 2D/Bi: 20 3D/Uni: 100 3D/Bi:100	NS	NS	NS	NS
Rotten[31] (2004)*	All data of cleft cases detected by US (1996–2002), Delafontaine Hospital, Saint Denis, France	96	22–39 (mean, 28.2 ± 4.1)	Cases of isolated CL ± P	No performed reference test (pathology or surgical report)	NS	NS	2D/Uni: 27/31 2D/Bi:2/3	2D/Uni: 87 2D/Bi: 66	2D/Uni: 37/42 2D/Bi: 18/20	2D/Uni: 88 2D/Bi: 90	NS	NS
Hanikeri[30] (2006)	CLP unit, Princess Margaret Hospital, Perth, Australia: questionnaires to referred parents	216	15–20 (80.5%)	Children born and treated for cleft in November 2000 or September 2003	False-positive diagnosis; intrauterine death; TOP	2D/Uni:39/96 2D/Bi: 8/18	2D/Uni: 41 2D/Bi: 44	NS	NS	NS	NS	0/95	0
Prospective studies													
Johnson[33] (2000)*	Three referral centers, South Carolina, USA: consecutive cases of cleft†	31	15–35 (mean, 24.8 ± 5.0)	Fetuses suspected of having facial cleft	False-positive diagnosis	NS	NS	2D: 26/28 3D: 28/28	2D: 93 3D: 100	2D: 9/22 3D: 19/22	2D: 41 3D: 86	NS	NS
Chmait[32] (2002)*	Fetal Diagnosis and Treatment Center, San Diego, USA: consecutive referred women (1994–2001)	57	15–35 (mean 24.6 ± 5.2)	Referral on suspicion of cleft; positive family history	NS	NS	NS	2D: 41/45 3D: 45/45	2D: 91 3D: 100	2D: 19/41 3D: 37/41	2D: 46 3D: 90	NS	NS
Wang[34] (2007)	All cases referred for suspected facial cleft, Tsan Yuk Hospital, Hong Kong	30	16–36 (mean, 26)	Suspected or confirmed facial cleft on 2D ultrasound	NS	NS	NS	2D: 21/22 3D: 22/22	2D: 96 3D: 100	NS	NS	2D: 2/9 3D: 8/9	2D:22 3D:89

Only the first author's name of each study is given. The index text included two-dimensional (2D) and three-dimensional (3D) ultrasound in all studies. *The reported CL ± P cases for Rotten and Levaillant[31], Johnson *et al.*[33] and Chmait *et al.*[32] were CL only. †Details of study time and duration were not given by Johnson *et al.*[33]. Bi, bilateral; GA, gestational age; CLP, cleft palate with cleft lip; NS, not stated; TOP, termination of pregnancy; Uni, unilateral; USA, United States of America.

5

Prenatal ultrasound screening for orofacial clefts

Ultrasound Obstet Gynecol 2011; 38: 434–439

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ABSTRACT

Objectives To evaluate the sensitivity and specificity of ultrasound for detecting prenatal facial clefts in low-risk and high-risk populations.

Methods This study prospectively followed up a non- selected population, namely all pregnant women who underwent routine second-trimester prenatal ultrasound screening in the Utrecht region during the 2-year period from January 2007 to December 2008.

Results A total of 35 924 low-risk and 2836 high- risk pregnant women underwent ultrasound screening. Orofacial clefts were present in 62 cases, an incidence of 1: 624. The distribution of clefts was as follows: 18 (29%) cleft lip, 25 (40%) cleft lip with cleft palate, 17 (27%) cleft palate only, one median cleft and one atypical cleft. Of these, 38 (61%) were unilateral and 23 (37%) were bilateral. Thirty-nine per cent (24/62) had associated anomalies, with most chromosomal defects found in the cleft lip with cleft palate and cleft palate only groups. Cleft lip with or without cleft palate was detected prenatally in 38/43 cases, a sensitivity of 88%. No case of cleft palate only was detected prenatally. There were three false- positive cases, of which two were fetuses with multiple congenital deformities.

Conclusions Ultrasound screening has a high sensitivity for the detection of cleft lip with and without cleft palate in high-risk and low-risk pregnancies in our region, where well-trained sonographers carry out primary screening. The key to a high sensitivity of prenatal ultrasound is likely to be a combination of excellent training of sonographers, referral to specialized centers when a cleft is suspected, routine visualization of the fetal face and advances in ultrasound techniques.

INTRODUCTION

In The Netherlands, transabdominal two-dimensional (2D) ultrasound screening during the second trimester of pregnancy was made universally accessible by legislation and health insurance coverage in 2007. Evaluation of the upper lip for possible cleft lip and palate is an optional element in this screening (NVOG Dutch Society of Obstetrics & Gynecology protocol[1]). With an incidence of cleft lip with or without cleft palate (CL ± P) and cleft palate only (CP) of 1.8 per 1000 births[2], this translates to approximately 320 cases of orofacial cleft per year in The Netherlands[3]. As 90 – 95% of Dutch pregnant women undergo ultrasound screening, cleft palate teams are commonly confronted with prenatally diagnosed clefts.

Classification of orofacial clefts diagnosed by ultra- sound is generally carried out according to the system of Nyberg *et al.*[4]. However, in this classification no distinction is made between the alveolus and the hard palate, which, in the presence of CL, can be important in the detection of an additional CP. Proper classification is essential because different types of cleft may be variably associated with additional anomalies and chromosomal disorders[4–7], while isolated clefts are associated with low mortality and morbidity rates and are primarily a functional and esthetic problem[8].

In a recently published systematic review it was concluded that transabdominal 2D ultrasound screening in a low-risk population has a relatively low rate of detection of orofacial clefts[8], with detection rates of 23 – 58% in the most recent large prospective studies[9,10]. Moreover, in most studies reporting on the accuracy of ultrasound screening, inconsistent methodological quality is observed. In this prospective cohort study, the sensitivity and specificity of ultrasound in detecting orofacial clefts during prenatal screening in a low-risk and a high-risk population is presented, as well as the percentage of associated anomalies per type of orofacial cleft.

METHODS

This prospective follow-up study investigated the detection of orofacial clefts by ultrasound screening in The Netherlands during the period of January 2007 to December 2008. For the purpose of screening, The Netherlands is subdivided into eight regions, in which trained midwives, sonographers and obstetricians perform routine 2D ultrasound screening in several centers. Every region has one main referral center to which pregnant women are referred if an abnormality is suspected. Upon referral, certified obstetricians perform further 2D and three-dimensional (3D) ultrasound examinations, and the patient is counseled by members of the cleft palate team[11]. The standard for advanced 2D ultrasound examination is set by the Dutch Society for Gynaecology and Obstetrics (NVOG), the documentation of which is available electronically[1]. Ultrasound screening routinely includes detailed examination for orofacial clefts.

Study population

The study cohort comprised all screened pregnant women in the geographically well-defined screening region of Utrecht. The study population was divided into a low-risk population and a high-risk population. This separation was made to ensure that all pregnant women in each group had a comparable *a priori* risk. Pregnant women who underwent routine screening formed the low-risk population, and the high-risk population consisted of pregnant women with a positive family history of orofacial cleft or other risk factors for fetal abnormalities. The high- risk population and fetuses suspected of orofacial cleft were seen in a tertiary referral center (the Wilhelmina Children's Hospital). When an associated anomaly was detected, karyotyping by amniocentesis and consultation with a clinical geneticist was recommended. When parents opted for termination of pregnancy (TOP), mostly because of the presence of associated anomalies, an autopsy was recommended to verify the prenatal diagnosis. When parents opted to continue a pregnancy, they met a multidisciplinary team, which included an obstetrician and two members of the cleft palate team: a plastic surgeon and a medical psychologist. In the first week after delivery all newborns were examined by a plastic surgeon and a pediatrician or a clinical geneticist from the cleft palate team to verify prenatally detected orofacial clefts. Newborns in the region of Utrecht

who had an orofacial cleft that was undiagnosed prenatally were referred to the cleft palate team at the Wilhelmina Children's Hospital and evaluated at the cleft clinic within 2 weeks after delivery.

Data on all ultrasound examinations were retrieved from the screening centers where data were stored electronically (MOSOS version 7 – 9, Copyright @ 1988 – 2009; Bureau Medische Automatisering, Houten, The Netherlands). Postnatal data were retrieved from the clinical records of the cleft palate team. Statistical analysis was performed on anonymized data using SPSS statistical software (Version 14; SPSS Inc., Chicago, IL, USA). The significance level was set at $P < 0.05$.

RESULTS

During the 2-year study period a total of 35 924 low-risk pregnant women and 2836 high-risk pregnant women underwent ultrasound screening in one of the 25 non-profit centers belonging to the Wilhelmina's Children's Hospital referral network. The resulting study population of 38 760 women represented 93% of the total pregnant population of 41 482.

Sixty-two fetuses (liveborn, stillborn or TOP before 24 weeks) with confirmed orofacial clefts were identified in the study population. This resulted in a prevalence of 1.6 per 1000 fetuses (including isolated and associated cases). For liveborn infants the prevalence in this group was 1.42. The distribution in the total population was 29% (18/62) cleft lip (CL), 40% (25/62) cleft lip with cleft palate (CLP), 27% (17/62) CP, one median cleft and one atypical cleft (4%) (Table 1). Male to female ratios for each cleft type are shown in Table 2. The median gestational age at detection of an orofacial cleft was 21 (range, 18 – 23) weeks of gestation. An additional five cases of facial cleft were identified postnatally by the cleft palate team in patients whose mothers had not undergone prenatal ultrasound screening.

Table 1

Cleft type	*n*	*Prevalence per 1000**	*Sensitivity low risk (%)*	*False positive cases*	*Sensitivity high risk (%)*	*False positive cases*
CL	18	0.44	81 (13/16)	1	100 (2/2)	0
CLP	25	0.60	91 (20/22)‡	0	100 (3/3) ‡	1
CP	17	0.41	0 (0/14)	0	0 (0/3)	1
MC†	1	0.03	100 (1/1)	0	-	-
Atypical cleft	1	0.03	100 (1/1)	-	-	-
Postnatal only¶	5	0.12	-	-	-	-
Total	**62**	**1.63**	**67 (36/54)**	**1**	**62.5 (5/8)**	**2**

* including stillbirths, terminations and live births † Median cleft ‡ In the group of correctly diagnosed CLP there were in total 7 cases were a cleft lip was detected, but an associated cleft palate was missed (6 in the low risk- and 1 in the high risk group) ¶ detected postnatal only because parents did not opt for prenatal screening

Table 2

Cleft type	*n*	*Male/female ratio*
CL	18	1.6:1
CLP	25	3.5:1
CP	17	0.9:1
Total	**60**	**1.8:1**

Twelve of the 62 fetuses (19%) with orofacial cleft in the study population had a positive family history; in nine cases there was a first-degree relative (mother, father or sibling) with a CL ± P and in three cases a second-degree relative (aunt, uncle or cousin). Seven pregnant women with a positive family history, and so who should have been referred directly to a specialized center and screened as high risk, were screened in the low-risk clinics (four had first-degree and three had second-degree relatives with facial clefting).

Detection rates

Low-risk population

A total of 54 fetuses with clefts were in the low-risk population (Table 1). There were 14 cases of CP, none of which was diagnosed prenatally. CL was detected prenatally in 13/16 cases, giving a sensitivity of 81% (95% CI, 56 – 94%). Two false-positive cases were detected in the low-risk group. One case was a fetus with multiple congenital anomalies, and karyotyping showed trisomy 13. The parents decided on TOP and the

facial cleft was not confirmed by autopsy. In the second case a CP was suspected after screening by 2D ultrasound. A normal lip and palate were observed on specialized ultrasound scans in the Wilhelmina's Children's Hospital and this was confirmed postnatally. CLP was detected prenatally in 20/22 cases, giving a sensitivity of 91% (95% CI, 69 – 98%). One case of midline cleft was correctly detected during screening, along with additional anomalies (hypertelorism, agenesis of the corpus callosum or encephalocele). One fetus had a Tessier IV cleft with microphthalmia, and the parents decided on TOP.

High-risk population

A total of eight fetuses with clefts were in the high-risk population. They all underwent at least two 2D and 3D second-trimester scans in the Wilhelmina Children's Hospital. There were three cases of CP, none of which was diagnosed prenatally (Table 1). CL was detected prenatally in 2/2 cases and CLP was detected in 3/3 cases, giving a sensitivity of 100% (95% CI, 38 – 100%) in both groups. There was one false-positive case, concerning a fetus with multiple congenital anomalies and trisomy 18, in which the parents decided on TOP and the CLP was not confirmed during autopsy.

Associated anomalies

Of 62 fetuses with a facial cleft, 24 (39%) had associated anomalies (Table 3). CL had a low percentage (17% (3/18)) of associated anomalies, whereas bilateral CLP and CP had much higher incidences of associated anomalies (57% and 53%, respectively).

There were eight cases with chromosomal abnormalities, in six of which prenatal karyotyping had been performed for suspicious ultrasound findings; in the remaining two cases the diagnosis was made postnatally. The association of chromosomal and syndromal anomalies in each group of facial cleft type is shown in Table 4. Trisomy 18 was the most common chromosomal defect observed. Almost all syndrome diagnoses were in the group of CP, with an incidence of nine out of 17 (53%) in this group. One case of Goldenhar syndrome was diagnosed in combination with a Tessier IV cleft. In the CP group there were three fetuses with Robin sequence. Figure 1 shows the incidence of chromosomal anomalies according to the type of cleft and the presence

or absence of additional anomalies on prenatal ultrasound screening, illustrating the risk of missing a diagnosis of a chromosomal anomaly in these cases. In the group of bilateral CLP, trisomy 18 was diagnosed postnatally and no associated anomalies were observed on ultrasound.

Outcome

Fifty-four infants (87%) were born alive (Table 3). TOP was performed in five cases. In all but one terminated fetus there were severe associated anomalies present, the exception being a case of isolated CLP. Three cases of intrauterine death were registered in fetuses with trisomies 13 (n = 1) and 18 (n = 2). All surviving infants were still alive at the time of writing and under the care of the cleft palate team.

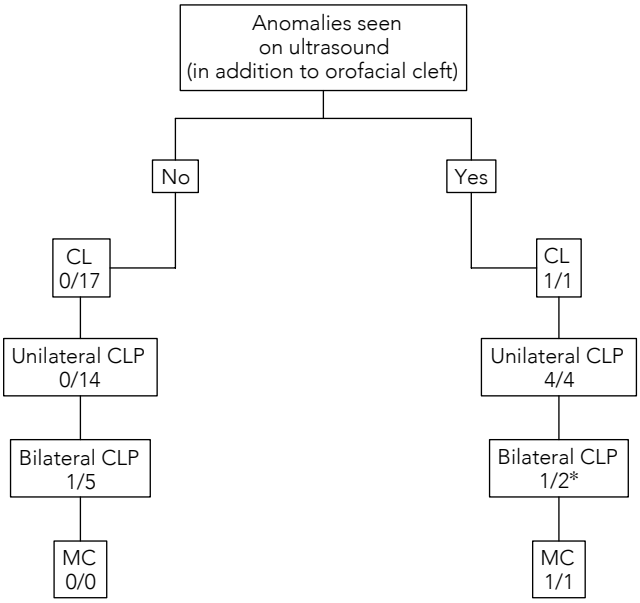

Figure 1 *Incidence of chromosomal anomalies according to type of cleft and presence or absence of additional anomalies on prenatal ultrasound screening, illustrating the risk of missing a diagnosis of a chromosomal anomaly in these cases. *In one case with trisomy 18 and bilateral cleft lip with cleft palate (CLP), the anomalies and CLP were missed on ultrasound at 20 weeks, although they were detected on ultrasound at > 24 weeks of gestation. CL, cleft lip; MC, median cleft.*

Table 3

Cleft type	*Isolated n (%)*					*Associated n(%)*				
	n	Prenatally detected (n)	TOP (n)	IUD (n)	Postpartum Death (n)	n	Prenatally detected (n)	TOP (n)	IUD (n)	Postpartum death (n)
CL	15(83)	13	-	-	-	3 (17)	2	1	-	-
CLP	12(67)	11	-	-	-	6 (33)	6	2	1	-
CLP (bi)	3 (43)	3	1	-	-	4 (57)	3	-	2	
CP	8 (47)	0	-	-	-	9 (53)	0	-	-	-
MC	-	-	-	-	-	1(100)	1	-	-	-
Atypical	-	-	-	-	-	1 (100)	1	1	-	-
Total	**38/62 (61%)**		**1**	**-**	**-**	**24/62 (39%)**		**4**	**3**	**0**

Table 4

Cleft type	*Anomaly*	*Syndromes/Sequence*	*Chromosomal defects*	*Prenatally detected*
CL	1 Umbilical hernia			No
	1 club foot			No
			1 trisomy 18	Yes
Unilateral CLP	1 hypospadia			No
	1 Hirschsprung's disease			No
	1 VSD*		1 trisomy 21	Both Yes
			3 trisomy 18	Yes (3x)
Bilateral CLP	1 Hypertelorism, agenesis corpus callosum			Yes
			Trisomy 13	Yes
			Trisomy 9P	No
			Trisomy 18	No
CP		3 Pierre Robin		No (2)† , Yes (1)
		2 Stickler syndrome		No (2)
		2 Kabuki syndrome		No (2) ‡
		1 vd Woude syndrome		No
		1 Beckwith Wiedemann syndrome		No§
MC	1 Hypertelorism, agenesis corpus callosum, encepahalocele			Yes
Atypical cleft	1 Tessier IV cleft and microthalmia	Goldenhar syndrome		Yes

*ventricular septal defect † in one case on US club foot ‡ In one case on US a oligohydramnios § On US amniotic hernia

DISCUSSION

Through introduction of routine prenatal screening, cleft palate teams are more frequently confronted with prenatally diagnosed clefts. Increased awareness of facial clefting and associated anomalies might clarify pregnancy options. When a diagnosis is made, parents have the opportunity to prepare themselves emotionally and practically[12] by meeting a multidisciplinary team consisting of an obstetrician, a psychologist and a plastic surgeon. This allows the parents to discuss the surgical options as well as the demands of a growing child with a cleft lip and palate.

This prospective study of ultrasound screening demonstrates a sensitivity of 88% for CL ± P; however, the overall sensitivity for orofacial clefts was lower – 65% in the

low-risk group and 62.5% in the high-risk group – because no cases of isolated CP were diagnosed prenatally. Pregnant women for whom there was suspicion of a fetal facial cleft were referred to a referral center for 2D and 3D ultrasound scans where obstetricians detected additional cleft palates in three of six cases (50%) in which there was initially a cleft only lip identified by primary ultrasound. These rates are high in comparison with former studies that reported variable orofacial cleft detection rates of 23 – 59.6% on 2D ultrasound and 66 – 100% on 3D ultrasound[8,13]. In our study, sources of bias were minimized by determining the diagnostic accuracy of screening tests[8]. A large study population in a well-defined geographic area was prospectively enrolled. Also, high-risk and low-risk pregnant women were studied separately. The relative risk of familial recurrence was recently reported to be 32 (95% CI, 24.6 – 40.3) for any CL in first-degree relatives and 56 (95% CI, 37.2 – 84.8) for cleft palate alone[14,15]. Postnatal follow-up was at least 1 year, long enough to detect the majority of associated anomalies. Ultrasound evaluation of the study population was carried out according to a standardized protocol. To perform routine prenatal screening, minimal quality criteria were set for sonographers (with a minimum of 150 – 200 examinations annually)[11]. Consequently, obstetricians performing ultrasound examinations in a high-risk setting have more experience and the opportunity to use 3D ultrasound techniques, which resulted in the detection of additional cleft palates in three of six cases (50%). This is in concordance with Crane et al., who reported significantly higher detection rates in tertiary centers vs. non-tertiary centers[16].

Three cases of false-positive diagnoses were identified; in two fetuses with multiple congenital anomalies and trisomy 13 and 18, respectively, an ultrasound diagnosis of CLP was not confirmed by autopsy. In the third case, CP was suspected on screening by 2D ultrasound, but subsequent referral revealed no CP on specialized ultrasound. The specificity of prenatal ultrasound will be high because of the large group of true negatives and it is therefore not informative to calculate diagnostic accuracy. The impact of a falsely diagnosed anomaly can be severe. It is important to differentiate correctly between different types of facial clefts because they are variously associated with additional anomalies[4,6,7]. Previous pre- natal studies have quoted rates of from 0%[6] to 20%[4] for CL, 24%[7] to 52%[6] for unilateral CLP and 48%[7] to 79%[6] for bilateral clefting, which are in concordance with our results. Cases of CL were associated with

almost no chromosomal or syndromal defects (6%), CLP (especially bilateral) had 28% chromosomal or syndromal defects and CP had a high percentage of syndromal defects (53%) but no chromosomal defects. The percentage of associated anomalies is higher in cases with prenatally detected orofacial clefts than in those only identified postnatally, because of spontaneous fetal death and medical intervention. Eighty-eight percent of the chromosomal defects were detected prenatally, with one case of trisomy 18 missed. Additional anomalies in cases with chromosomal defects are usually more evident and detection of one should prompt more detailed screening, also leading to increased detection of orofacial clefts. As different types of orofacial cleft are variously associated with additional anomalies, not every pregnant woman with a diagnosis of a cleft should receive further prenatal invasive testing owing to the minor risk of miscarriage. All patients with detected clefts should be referred to a clinical geneticist. There is a minor chance (3%) of chromosomal abnormality when no associated anomalies are diagnosed, in agreement with a recent study by Gillham et al.[13]. Therefore, we advise no further analysis in cases with suspected isolated CL. In isolated CLP, one should be cautious with invasive diagnostics. When associated anomalies are detected before 24 weeks, one should discuss the option of karyotyping and multiplex ligation-dependent probe amplification (MLPA) for 22q11 deletions and fluorescence in-situ hybridization (FISH) (a molecular cytogenetic technique used to detect chromosomal microdeletions that may be missed on routine chromosome analysis)[17]. As median clefting is never found in isolation, cytogenetic and molecular diagnostic analysis should be offered.

The consequences of routine ultrasound at 20 weeks of gestation are the subject of ongoing political discussion in The Netherlands. Recently, the numbers of terminations performed in the hospital setting in the second trimester (12 – 24 weeks) were published, revealing an increase of 140 (7.4% of all TOPs) to 270 (11.5% of all TOPs) in 2005 – 2007, after the introduction of standard ultrasound scans[18]. However the trend towards more hospital terminations (i.e. on medical grounds) started in 2003 and is attributed to the increase in ultrasound screening, even before the current legislation was introduced[18]. Moreover, termination for isolated CL ± P remains uncommon in The Netherlands. In the region of Utrecht, TOP for isolated orofacial clefting occurred only once in this period. Apparently, parental consideration is different in terms of minor and major

deformities, especially when a deformity is readily amenable to reconstruction[19].

In conclusion, this study cohort of a non-selected population of 38 760 pregnant women included 62 fetuses with facial clefts. Thirty-nine per cent of these had associated anomalies. There was a high sensitivity of detecting orofacial clefts by ultrasound screening. The high rate of detection of an orofacial cleft is probably a result of the excellent training and experience of the sonographers, referral to specialized centers when a cleft is suspected, routine visualization of the fetal face and advances in ultrasound techniques. Different types of orofacial cleft relate differently to associated anomalies and thus to ultimate outcome. For this reason, pregnancies in which there is suspicion of a fetal cleft with associated anomalies should be routinely referred for further genetic analysis.

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The accuracy of prenatal ultrasound in determining the type of orofacial cleft

Prenatal Diagnosis, 2015, Feb 26. [Epub ahead of print]

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ABSTRACT

Objectives The aim of this study was to assess the accuracy of prenatal transabdominal ultrasound in determining the oral cleft type.

Methods A retrospective cohort study was performed on all consecutive cases of orofacial cleft diagnosed by prenatal ultrasound examination in the Wilhelmina Children's Hospital, a tertiary referral hospital, between January 2002 and December 2012. Prenatal findings were compared to postnatal diagnoses.

Results 134 patients were included. The mean gestational age at ultrasound examination was 24 weeks + 5 days. Prenatal diagnosis was in accordance with postnatal findings in 76.9% of cases (103/134) with regard to the cleft type. Underestimation of the cleft occurred in 19.4% (26/134), whereas in 3.7% (5/134) the extent was overestimated. In distinguishing bilateral from unilateral clefts, no errors were made.

Conclusion Prenatal ultrasound is accurate in assessing the types of orofacial clefts in a large majority of the cases and is completely accurate in distinguishing between uni- and bilateral clefts. This study indicates that it is a reliable technique to assess the cleft type, which is important for counseling future parents. Although, the clinician should be aware of the fact that a cleft palate is easily missed, and subsequently underestimation of cleft extend is frequent.

INTRODUCTION

Orofacial clefts (OFCs) are common craniofacial malformations.[1] In the Netherlands, their combined incidence is about 1.8 per 1000 live births per year, resulting in approximately 320 cases of OFC per year.[2] OFCs can be categorized in different subtypes, however a subdivision of three subtypes is most frequently described: cleft lip (CL), cleft lip and palate (CLP) and isolated cleft palate (CP). To make a better assessment of the prenatal diagnosis in this study, involvement of the alveolus (CLA) was also assessed since this is of importance in counseling future parents.

The distribution of cleft type differs per country. In the Netherlands the distribution was reported to be 29% CL, 40% CLP and 27% CP. 61% of the clefts were unilateral and 37% bilateral.[3] The distribution of clefts in Canada was reported to be 17% CL, 42% CLP and 41% CP.[4] Canadian data report that clefts were 24% bilateral, 24% unilateral right and 52% unilateral left.[5] Ultrasonographers and cleft and palate teams (consisting of an obstetrician, plastic surgeon, psychologist and clinical geneticist) are commonly confronted with prenatally diagnosed clefts nowadays.[3] Firstly, this could be attributed to the increased number of women undergoing ultrasound (US) screening during the second trimester of pregnancy since a countrywide screening programme was introduced by legislation and insurance in the Netherlands in 2007. This programme has now become standard care, resulting in a 90-95% participation of all pregnant women in the Netherlands. Secondly, it could be attributed to the improved detection as reported in different studies concerning the accuracy in prenatally detecting OFCs.[6]

An accurate prenatal diagnosis is of upmost importance in counseling future parents on prenatal findings and to enable parents to prepare themselves in an emotional and practical way.[7] It is important for parents to know what to expect from the physical appearance of their child and the trajectory that has to be undertaken in the hospital after birth. Furthermore, prenatal differentiation between the various types of cleft is important because the different OFC types are associated with various other congenital anomalies and chromosomal abnormalities[8] of which some have a great impact on fetal prognosis with regard to morbidity and mortality.[9]

Different studies show a wide range in results concerning the prevalence of congenital anomalies associated with OFCs, e.g. malformations of the limbs and congenital heart

diseases. In CL the prevalence of an associated congenital anomaly is lowest and ranges from 7.6-41.4%.[10] Concerning CLP, the frequency is higher and ranges from 21.1-61.2%. CP is the category most frequently associated with additional congenital anomalies with a prevalence ranging from 22.2-78.3%.[10] Chromosomal abnormalities are most frequently seen in association with additional anomalies. In the absence of associated anomalies, chromosomal defects are found postnatally in 1.8% of patients with CL, 1.0% of patients with CLP (1.0%) and 1.6% of patients CP (1.6%).[10]

Despite the increased number of women undergoing US screening combined with the improved accuracy in detecting OFCs and the known importance of correct prenatal diagnosis, no sufficient research has been done on the accuracy of prenatal US in determining the type of cleft. Therefore, the aim of this study was to assess the accuracy of the oral cleft type diagnosis in the prenatal period.

METHODS

For the purpose of screening in the second trimester of pregnancy, The Netherlands is divided into eight well-defined regions in which ultrasonographers, obstetricians and trained midwives perform US examination in several centers. In the screening region of Utrecht, the Wilhelmina Children's Hospital is the main referral center to which pregnant women are referred if an abnormality is suspected. Upon referral, four certified obstetricians of the department of Obstetrics and Gynecology perform further examination including detailed examination for OFCs. When a cleft is diagnosed, patients are counselled on amniocentesis for genetic testing and if associated anomalies are detected, consultation with a clinical geneticist is recommended. Furthermore, the parents are invited to the so-called "Prenatal Cleft Clinic", where they are seen by the cleft lip and palate team. They offer the parents further information and detailed counseling about the possible consequences of having an OFC. When parents opt for termination of pregnancy (if for medical reasons, the upper limit is 24 weeks in the Netherlands), an autopsy is recommended to verify the prenatal diagnosis. In this study, patients with an OFC diagnosed by prenatal US examination in the Wilhelmina Children's Hospital, between January 2002 and December 2012, were included. The

initial evaluation was performed within a week from diagnosis by a screening clinic and was done by a fetal medicine specialist. All examinations were carried out trans abdominally using a General Electric Voluson730 Expert equipped with a RAB4-8L probe or a E8 US system equipped with a RAB4-8D probe (GE Medical Sytems, Kretz US, Zipf, Austria). The main focus of the US examination was to exclude associated fetal anomalies, and to provide a first assessment of the extent of the OFC. A follow-up evaluation by the fetal medicine specialist was done within four weeks, with the same ultrasound equipment, and in the presence of a plastic paediatric surgeon. The main purpose of this evaluation was to determine the extent of the OFC. When the cleft was limited to the lip, hence with intact alveolar ridge, the cases were classified as CL. If there was a discontinuity of the maxillary arch frontal of the foramen incisivum but the palate seemed intact, the cases were classified as CLA. If the lip, alveolus and palate seemed affected the cases were classified as CLP. If the lip and alveolar ridge seemed intact and there was suspicion of an affected palate the cases were classified as CP. Furthermore it was described whether the cleft was uni- or bilateral. 2D US was performed in all cases and an additional 3D US was performed if the fetus was in a good position. In this study we included the cleft diagnosis of the last scan that was performed. Patients with major associated anomalies (e.g. trisomy 13/18) were excluded since the cleft was subordinate to other malformations and therefore not well described. The US data were retrieved from the electronic information system developed to record and process the US measurement and images from obstetrical examinations (MOSOS; U; Version 11.0, BMA, Houten, the Netherlands).

Postnatal diagnoses were retrieved from electronic clinical records reported by the cleft lip and palate team. Medical ethical board approval was obtained for this study. All data were collected in a database. Prenatal diagnoses were compared with postnatal findings. Accuracy of prenatal US was calculated based on postnatal definitive diagnoses.

RESULTS

139 patients with an oral cleft type diagnosis in the prenatal period were included. Subsequently, five patients with major associated anomalies were excluded. Of the remaining patients, 64% (86/134) were male and 36% (48/134) female. The distribution of the OFCs as seen at birth was as follows: CL: 21.6% (29/134), CLA: 12.7% (17/134), CLP: 61.9% (83/134), CP: 3.7% (5/134) (see table 1).

Table 1. *The distribution of the orofacial clefts and the patient characteristics as seen at birth*

		n (%)
Cleft type	CL	29 (21.6)
	CLA	17 (12.7)
	CLP	83 (61.9)
	CP	5 (3.7)
Location	Unilateral	112 (83.6)
	Bilateral	22 (16.4)
Sex	Male	86 (64.2)
	Female	48 (35.8)

CL = cleft lip, CLA = cleft lip and alveolus, CLP = cleft lip/alveolus and palate, CP = cleft palate only. Unilateral = unilateral clefts and cleft palates only

The prenatal diagnosis with regard to the type of the cleft was consistent with postnatal findings in 76.9% (103/134). Underestimation of the cleft occurred in 19.4% (26/134) and in 3.7% (5/134) the cleft was overestimated (see table 2).

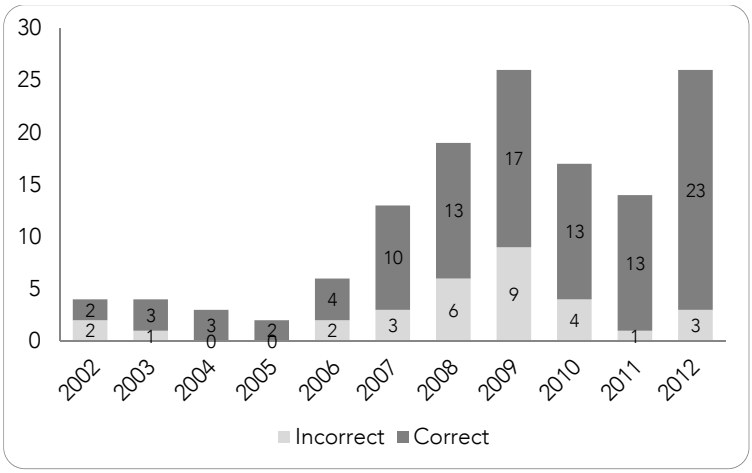
Table 2. *Prenatal versus postnatal diagnosis with regard to the cleft type*

			Postnatal diagnosis		
			Correctly diagnosed clefts	Underestimated clefts (true diagnosis)	Overestimated clefts (true diagnosis)
Prenatal diagnosis	CL	50	29	-	21 (9 CLA, 12 CLP)
	CLA	8	3	-	5 (CLP)
	CLP	71	66	5 (CLA)	-
	CP	5	5	-	-
	Total	134	103 (76.9%)	5 (3.7%)	26 (19.4%)

Correctly diagnosed clefts: 76.9% (103/134), underestimated clefts: 19.4% (26/134), over-estimated clefts: 3.7% (5/134). CL = cleft lip, CLA = cleft lip and alveolus, CLP = cleft lip/alveolus and palate, CP = cleft palate only.

Particularly CL was often found to be more extended than prenatally predicted: in nine cases the alveolus appeared to be involved; in 12 cases involvement of the palate was missed. Concerning CLA five cases appeared to be CLP at birth. Overestimation of the extent of the cleft occurred in five fetuses diagnosed with CLP of whom the palate appeared to be intact at birth. The distinction between bilateral (22/134) and unilateral (112/134) clefts was correct in all prenatal cases. The mean gestational age at time of diagnosis was 24 weeks + 5 days. Annual accuracy and frequency of prenatal diagnosed clefts over the 11-year study period are depicted in figure 1.

Figure 1. Annual accuracy and frequency of prenatal diagnosed clefts



The accuracy of the prenatal diagnosis per year; 2002: 50%, 2003: 75%, 2004: 100%, 2005: 100%, 2006: 67%, 2007: 77%, 2008: 68%, 2009: 65%, 2010: 77%, 2011: 93%, 2012: 89%

DISCUSSION

This study showed an accuracy of 76.9% in assessing the type of the OFC and 100% accuracy in distinguishing between uni- and bilateral clefts by means of prenatal transabdominal US. 26 of the 31 incorrectly diagnosed clefts appeared to be more extended at birth and in five cases the cleft was overestimated.

An accurate diagnosis is of upmost importance for counselling parents on prenatal findings and enabling parents to prepare themselves in an emotional and practical way.[7] Furthermore, an accurate diagnosis of cleft type is essential in determining the risk of severe associated congenital anomalies since different subtypes have a different correlation, as was mentioned in the introduction.[8,9]

Diagnosing a small indentation or incomplete cleft of the alveolus is extremely difficult. Involvement of the alveolus is of clinical importance because it often means a second operation, higher risk for a speaking disorder and dentofacial deformities. Therefore, we also included CLA in our analysis. This has resulted in "strict" analysis; if this differentiation is not made, the accuracy of US increases to 84%.

Accuracy rates of prenatal US are not consistent in literature. Berggren et al.11 reported an accuracy rate of prenatal US of 43.2% (19/44) and Demircioglu et al.[12] reported an accuracy of 75.0% (66/88). These differences can be explained by small study size, variation in study methods (multiple examiners and different US approaches) and/or the discrepancy in terminology used. In our study all US scans were performed by gynecologists specialized in advanced US examination in the Wilhelmina Children's Hospital. Yet in both studies[11, 12] the most common reported error was a more extensive cleft at birth than prenatally diagnosed, which was in line with our results.

A limitation of this study is the fact that the cases included may not be totally representative for all OFCs, since all cases were referrals from clefts identified at screening performed at a primary care setting. Subtle clefts may be missed at the referring centers and thus not seen at the Wilhelmina Children's Hospital. The clefts referred may be more severe and therefore it may be easier to assess the type of cleft. The examination could appear more thorough than if the general population was used.

In our study period US examination appeared to be unable to visualize the cleft palate. The abnormality of the palate was missed in 17 fetuses, even when the ultrasonographer was focused on the possibility of a cleft palate. Visualizing the palate is difficult since the palate has a dome-shaped structure and is surrounded by osseous structures. In 2010 Wilhelm et al.[13] described a method to visualize the palate by US; they state that an intact palate resembles an "equals sign" ultrasound pattern on US. In our study five (5/134) cases of isolated cleft palate were detected, of which three cases in 2011

and two cases in 2012. This detection in the last two years could be explained by the implementation of the Wilhelm"s method.

Over the years an increase in prenatally diagnosed clefts is seen (see figure 1) with 19 cases included before and 115 cases after the implementation of the universal US screening in 2007. This increase could be explained by the increased number of women undergoing US screening and the improved detection rate of OFCs.[6] With regard to defining the type of cleft, the accuracy presents a variable picture over the years with an average accuracy of 73.7% before 2007 and 77.4% from 2007-2012. Although data before 2007 are based on a low number of observations annually, we did not exclude these cases because there has not been a large change in technique or equipment to evaluate suspected clefts over those years. In the last two years of our study, US is more accurate (2011: 93%, 2012: 89%) in comparison to the first three years (2008: 68%, 2009: 65%, 2010: 77%) since the introduction of the screening programme in 2007. The improvement could be explained by the implementation of the earlier mentioned Wilhelm"s sign in 2010. Improvement in expertise and better skills of the ultrasonographers might also attribute to the increase in accuracy. To assess whether or not this trend will continue, we have to perform further study with longer follow-up. This study doesn't compare different techniques used for imaging the fetal palate but was limited to test the validity of the existing techniques used by the Wilhelmina's Children's Hospital cleft team. Determining whether or not the palate is involved when clefting of the lip and alveolus are found requires different methods like "3D reverse face view" revealed by Campbell et al.[14]. This technique allows a relatively straightforward assessment of the fetal palate with a high degree of accuracy (8/8 = 100%; 95% ci 62.8- 100.0%). Moreover, Sommerlad et al.[15] also describes methods to more accurately diagnose a cleft of the alveolar ridge. To improve the accuracy of US in determining the type of cleft future research should investigate other techniques, e.g. transvaginal US or 4th dimension US.

CONCLUSION

Prenatal ultrasound is accurate in assessing the types of orofacial clefts in a large majority of the cases and is completely accurate in distinguishing between uni- and bilateral clefts. This study indicates that it is a reliable technique to assess the cleft type, which is important for counseling future parents. Although, the clinician should be aware of the fact that a cleft palate is easily missed, and subsequently underestimation of cleft extend occurs frequent.

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A systematic review of associated structural and chromosomal defects in oral clefts: when is prenatal genetic analysis indicated?

J Med Genet 2012; 49: 490–498

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ABSTRACT

Background Oral clefts—comprising cleft lip (CL), cleft lip with cleft palate (CLP), and cleft palate (CP)—are being diagnosed prenatally more frequently. Consequently, the need for accurate information on the risk of associated anomalies and chromosomal defects to aid in prenatal counselling is rising. This systematic review was conducted to investigate the prenatal and postnatal prevalence of associated anomalies and chromosomal defects related to cleft category, thereby providing a basis for prenatal counselling and prenatal invasive diagnostics.

Methods Online databases were searched for prenatal and postnatal studies on associated anomalies and chromosomal defects in clefts. Data from the literature were complemented with national validated data from the Dutch Oral Cleft Registry.

Results Twenty studies were included: three providing prenatal data, 13 providing postnatal data, and four providing both. Data from prenatal and postnatal studies showed that the prevalence of associated anomalies was lowest in CL (0–20.0% and 7.6–41.4%, respectively). For CLP, higher frequencies were found both prenatally (39.1–66.0%) and postnatally (21.1–61.2%). Although CP was barely detectable by ultrasound, it was the category most frequently associated with accompanying defects in postnatal studies (22.2–78.3%). Chromosomal abnormalities were most frequently seen in association with additional anomalies. In the absence of associated anomalies, chromosomal defects were found prenatally in CLP (3.9%) and postnatally in CL (1.8%, 22q11.2 deletions only), CLP (1.0%) and CP (1.6%).

Conclusions Prenatal counselling regarding prognosis and risk of chromosomal defects should be tailored to cleft category, and more importantly to the presence/absence of associated anomalies. Irrespective of cleft category, clinicians should advise invasive genetic testing if associated anomalies are seen prenatally. In the absence of associated anomalies, prenatal conventional karyotyping is not recommended in CL, although array comparative genomic hybridisation should be considered. In presumed isolated CLP or CP, prenatal invasive testing, preferably by array based methods, is recommended.

INTRODUCTION

Oral clefts—one of the most common congenital malformations in humans—arise in approximately 1 in 700 live births.[1] It is has been well established that, although clefts can be isolated anomalies, they are frequently associated with other congenital anomalies, often as part of a syndrome or chromosomal defect. Oral clefts are traditionally subdivided into two categories: cleft lip with or without cleft palate (CL±P), and cleft palate only (CP). However, recent studies have emphasized subdivision into three categories: cleft lip only (CL), cleft lip with cleft palate (CLP), and CP, because of differences concerning embryologic development, prevalence, risk factors, and associations with other congenital anomalies.[2–5] Although many studies have also included median cleft lip or atypical facial clefts as oral clefts, these anomalies should be considered as separate craniofacial anomalies because of their different pathogenesis.[9 10] As a result of advances in transabdominal two dimensional ultrasound technology and its routine use in obstetric practice, oral clefts with or without associated anomalies are being diagnosed prenatally more frequently.[11] Detection rates— predominantly on CL±P—increased from approximately 5% in the early 1980s to over 26% in the late 1990s,[12] and they are as high as 65% today.[13] Consequently, there is an increasing need for accurate information to aid in prenatal counselling. When informing parents on outcome and prognosis, the category of cleft as well as the presence of other congenital anomalies is crucial. In particular, the identification of an underlying chromosomal defect will influence prenatal counselling and the management of the pregnancy significantly. However, in clinical practice there is often discussion on whether further invasive tests should be performed prenatally to identify chromosomal defects.[14] It is unknown whether invasive diagnostics should be offered in all identified cleft cases, or should be limited to specific cleft categories or the presence of associated anomalies.

To allow informed decisions on invasive prenatal diagnostics, clinicians and parents need to be informed about the prevalence of associated anomalies and underlying chromosomal defects in clefts. However, the reported rates in prenatal cleft populations vary greatly between studies.[6–8 13–16] Furthermore, these findings may reflect selection bias,[17] as cases that are more likely to be diagnosed prenatally tend to be the more

severe cases with associated anomalies and chromosomal defects.[11] Nowadays, increasing numbers of isolated clefts— not accompanied by growth retardation or other prenatal complications—are identified in utero.[11] Therefore, both prenatal and postnatal studies have to be interpreted in order to provide accurate information on the frequencies of associated anomalies and the underlying chromosomal defects for future prenatal cleft populations.

This systematic review presents a comprehensive summary of the literature and complementary Dutch registry data on prenatal and postnatal findings of associated anomalies and chromosomal defects related to cleft category. The aim of this study was to provide a basis for prenatal counselling of future parents and to advise on invasive genetic diagnostics in prenatally detected oral clefts.

METHODS

Literature search

In August 2011, the PubMed database was systematically searched using the search string '(cleft) AND (abnormalities OR anomalies) AND (chromosomal OR syndrome)'. The search was limited to articles published in English after 31 December 1994. This restriction was applied because technologies to identify specific syndrome diagnoses and chromosomal abnormalities have been developed relatively recent. For example, fluorescence in situ hybridisation (FISH) was introduced in clinical practice in the early 1990s, enabling the detection of specific microdeletions.[18 19] Consequently, studies published before 1995 may have reported relatively underestimated rates of associated anomalies and chromosomal defects. The titles and abstracts of the citations were screened independently by two reviewers (MJB and WM) to identify potentially relevant papers for which full text publications were retrieved. Additional studies were found by crosschecking references. Studies were included if they presented data on oral clefts that were analysed prenatally and/or postnatally for associated anomalies and chromosomal defects, the latter preferably verified by karyotype. To ensure the quality and prevent our prenatal analysis from significant underreporting, we excluded prenatal studies in which several obvious structural defects (eg, anencephaly or

holoprosencephaly) had been missed by ultra- sound. Because of the ethnic variation in prevalence of clefts and their associated anomalies,[1 17] studies evaluating non-Caucasian populations (eg, Asian populations) were excluded to keep a homogeneous study population.

Complementary data

Comparison of the existing literature on congenital anomalies and chromosomal defects associated with oral clefts is restricted, particularly due to differences in methodology. For example, there is a considerable variation in definitions and classifications of clefts and their accompanying defects, as well as in sample sizes, data sources, methods of data collection, and follow-up periods between studies.[17] For this reason, we complemented our review of postnatal studies with national data from the Dutch Oral Cleft Registry (NVSCA). Since 1997, the 15 Dutch cleft palate teams have registered oral clefts and their associated anomalies, using a unique detailed recording system based on the embryology of the head and neck area. Because major as well as minor anomalies (including dysmorphic features) are recorded in detail, the NVSCA data can be fitted into any existing classification and are highly applicable for comparison with other studies. Moreover, a selection of registry data has recently been validated and completed by a review of medical data, after a median follow-up period of 5 years.[20–22] This selection of validated data was used to complement our analysis on associated anomalies and chromosomal defects in postnatally detected clefts.[22] In addition, the annual NVSCA reports 1997–2010 were used to provide an inventory of the different syndromes and chromosomal defects that had been identified postnatally.[23 24] The methods of registration and validation have been described in detail elsewhere.[5 20–22]

Data analysis

Data on associated anomalies and chromosomal defects were extracted from the selected articles and subdivided according to the three cleft categories: CL, CLP, and CP. Also, the validated and completed NVSCA data were further analysed according to these three categories.[22] For studies not distinguishing CL and CLP, the category of CL±P was used. Median cleft lip and atypical facial clefts were excluded because of their different pathogenesis.[9 10] For all cleft categories, frequencies of associated

congenital anomalies and chromosomal defects were deducted from the reported data and presented in numbers and percentages. For studies providing karyotype information for isolated and/or associated cases, we calculated separate rates of chromosomal defects among isolated (if available) and associated clefts.[6–8 13–15 22 25–27] If studies did not provide numbers of karyotyped cases, but reported routine karyotyping of associated clefts (as in daily practice), we assumed that the majority of associated clefts were karyotyped.[13 22] Likewise, if chromosomal defects were reported from retrospective registry data without information about the presence or absence of associated anomalies, we assumed that chromosomal analysis had been performed in associated cases only.[16 26 28–31] If no specific data on chromosomal anomalies were available for the three cleft categories,[32–36] total rates of associated anomalies were calculated. Theoretically, these numbers might also include chromosomal anomalies detected in isolated clefts, without other congenital anomalies. Where possible, prevalence data were also subdivided according to unilateral and bilateral clefts.[6–8 13 14 25] To specify the detected chromosomal anomalies, we made an inventory of the different syndromes and chromosomal defects that had been identified in clefts prenatally and/or postnatally. Due to great differences in methodology,[17] we were not able to perform a meta-analysis with these data. To provide more information about the reviewed studies and to illustrate the differences, we summarised the various study characteristics and designs, including the inclusion criteria and definitions of clefts and accompanying defects, as well as the sample sizes, data sources, and methods of data collection.

RESULTS

The literature search yielded 9540 citations. Initial screening by title identified 88 potentially relevant abstracts, including 20 studies meeting the inclusion criteria. Subsequently, one of these studies was excluded because obvious structural anomalies (eg, lobar holoprosencephaly and severe congenital heart anomalies) had been missed prenatally, which raised doubts about the quality of the performed prenatal ultrasounds.[37]

Including the NVSCA study,[22] the remaining studies comprised three studies providing relevant prenatal data,[6–8 13] seventeen studies providing relevant postnatal data,[22 25–36] and four studies providing both.[13–16] All studies with postnatal data had a follow-up period of at least one year. Although the studies of Stoll et al,[26] Vallino-Napoli et al,[29] and Walker et al[25] presented both prenatal and postnatal data, they were included only in the postnatal analysis for divergent reasons. First, the retrospective data of Stoll et al[26] did not allow extraction of frequencies of associated anomalies and chromosomal defects among prenatally detected clefts. Second, Vallino-Napoli et al[29] reported data on pregnancy outcome, but the prenatally detected cleft cases could not be identified from their data. Finally, Walker et al[25] evaluated anomalies that could theoretically have been detected by ultrasound instead of those that had actually been detected. The latter were not separately discussed in their paper. The various study characteristics and designs of the reviewed studies are presented in supplementary table 1.

Prenatally detected associated anomalies and chromosomal defects

In the seven prenatal studies, a total of 407 fetuses with oral clefts were analysed.[6–8 13–16] The prevalence of associated anomalies and chromosomal defects in prenatally detected clefts is summarised according to cleft category in table 1. In the CL category, three out of 23 fetuses had associated anomalies, comprising a cardiac defect with a situs inversus,[6] an umbilical hernia, and a clubfoot.[13] One of these three CL cases had a chromosomal defect (trisomy 18).[13] CLP showed the highest prevalence of associated anomalies (54.0%, range 39.1– 66.0%). For studies that grouped CL and CLP together as CL±P, the prevalence was somewhat lower (29.9%, range 17.2–57.1%). Only one study evaluated prenatally detected CP cases (n=2); both cases had associated anomalies as well as an underlying chromosomal defect.[7] In addition to the three cleft categories, studies distinguishing unilateral and bilateral clefts generally found a higher prevalence of associated anomalies and chromosomal defects in bilateral than in unilateral CLP or CL±P (table 2).

Analysis of chromosomal defects in isolated and associated clefts revealed that almost all chromosomal defects were associated with other congenital anomalies or ultrasound markers, such as intrauterine growth retardation (97.4%, 74/76; one case with a chromosomal defect not included, as information on associated anomalies was

not available, table 1).[6] For only two cases with chromosomal defects, no accompanying defects were found by ultrasound; one case showed a mosaic trisomy 226 and the other had a trisomy 18.[13] Consequently, the prevalence of chromosomal defects in cases with associated clefts was 50.7% (74/146), while it was 0.9% (2/212) in cases with formerly presumed isolated clefts. In studies specifying the detected chromosomal abnormalities, trisomy 13 (56.3%, 36/64) and trisomy 18 (29.7%, 19/64) were the most commonly observed defects.[6–8 13 14] Offerdal et al[15] and Russell et al[16] did not specify prenatally identified chromosomal defects in their study (n=8 and n=5, respectively).

Postnatally detected associated anomalies and chromosomal defects

Seventeen studies analysed a total of 28 953 infants with oral clefts.[13–16 22 25–36] Table 1 shows the prevalence of associated anomalies and chromosomal defects in postnatally detected clefts. Similar to the prenatal analysis, postnatal studies showed that CL was less frequently associated with accompanying defects than the other two cleft categories. The prevalence of associated anomalies in CL was approximately 10%, except for the study of Rozendaal et al (41.4%).[22] For CLP and CL±P, most studies showed a prevalence of approximately 25%. However, the studies of Shaw et al[35] and Rozendaal et al[22] found a prevalence of about 60%. All studies reported that CP was the category most frequently associated with additional anomalies (45.9%; range 22.2–78.3%). When analysing the underlying chromosomal defects, the prevalence was highest in CL±P (9.5%, range 0.5–12.6%). The lowest prevalence of chromosomal defects was found in CL (1.4%, range 0–3.4%). Studies distinguishing unilateral and bilateral clefts showed a higher prevalence among bilateral than unilateral CLP (table 2).

Analysis of chromosomal defects in isolated and associated clefts revealed that almost all chromosomal abnormalities were found in association with additional anomalies. Only two studies found chromosomal defects in isolated clefts. In the study of Rittler et al,[27] information was available for 58% (108/185) of the isolated cleft cases (supplementary table 1).

Table 1. *Summary of published prevalence data on associated anomalies and chromosomal defects in prenatally and postnatally detected oral clefts*

Study Type	Associated Anomalies		Chromosomal Defects					
			*Isolated clefts**		*Associated clefts**		*Total clefts**	
	%	(n)	%	(n)	%	(n)	%	(n)
Prenatal studies								
CL								
Nyberg 1995†	20.0	(1/5)			0.0	(0/1)‡	0.0	(0/5)
Berge 2001†	0.0	(0/3)	0.0	(0/3)	0.0	(0/0)	0.0	(0/3)
Maarse 2011†	13.3	(2/15)			50.0	(1/2)	6.7	(1/15)
Total	13.0	(3/23)	0.0	(0/3)	33.3	(1/3)	4.3	(1/23)
CLP								
Nyberg 1995†	45.7	(16/35)	5.3	(1/19)	50.0	(8/16)	25.7	(9/35)
Berge 2001†	66.0	(35/53)	0.0	(0/18)	68.6	(24/35)	46.3	(25/54)§
Maarse 2011†	39.1	(9/23)	7.1	(1/14)	66.7	(6/9)	30.4	(7/23)
Total	54.0	(60/111)	3.9	(2/51)	63.3	(38/60)	36.7	(41/112)§
CL±P								
Perrotin 2001†	35.7	(20/56)	0.0	(0/36)	55.0	(11/20)‡	19.6	(11/56)
Offerdal 2008	57.1	(20/35)			40.0	(8/20)	22.9	(8/35)
Russell 2008	51.7	(15/29)			33.3	(5/15)‡‖	17.2	(5/29)
Gillham 2009†	17.2	(26/151)	0.0	(0/122)	34.6	(9/26)	6.0	(9/151)
Total	29.9	(81/271)	0.0	(0/158)	40.7	(33/81)	12.2	(33/271)
CP								
Berge 2001†	100.0	(2/2)			100.0	(2/2)‡	100.0	(2/2)‡
Postnatal studies								
CL								
Kallen 1996	10.4	(212 /2029)			10.4	(22/212)‖	1.1	(22/2029)
Milerad 1997	8.0	(13/163)¶						
Walker 2001**	8.3	(7/84)			14.3	(1/7)	1.2	(1/84)
Calzolari 2007	13.6	(245/1806)			13.1	(32/245)‖	1.8	(32/1806)
Tan 2009	11.9	(8/67)			12.5	(1/8)‖	1.5	(1/67)
Maarse 2011	11.8	(2/17)			0.0	(0/2)	0.0	(0/17)
Rittler 2011	7.6	(9/119)	1.8	(2/110)††	22.2	(2/9)	3.4	(4/119)
Rozendaal 2012	41.4	(29/70)			0.0	(0/29)	0.0	(0/70)
Total	12.1	(525/4355)	1.8	(2/110)	11.3	(58/512)	1.4	(60/4192)
CLP								
Kallen 1996	25.3	(819/3232)			24.5	(201/819)‖	6.2	(201/3232)
Milerad 1997	28.0	(60/214)¶						
Walker 2001**	24.6	(44/179)			31.8	(14/44)	7.8	(14/179)
Calzolari 2007	23.8	(693/2913)			22.1	(153/693)‖	5.3	(153/2913)
Tan 2009	23.2	(22/95)			13.6	(3/22)‖	3.2	(3/95)

Table 1. *(Continued)*

Study Type	Associated Anomalies	Chromosomal Defects		
		*Isolated clefts**	*Associated clefts**	*Total clefts**
	% (n)	% (n)	% (n)	% (n)
Maarse 2011	21.1 (4/19)		25.0 (1/4)	5.3 (1/19)
Rittler 2011	23.5 (93/395)	1.0 (3/302)††	28.0 (26/93)	7.3 (29/395)
Rozendaal 2012	61.2 (60/98)		5.0 (3/60)	3.1 (3/98)
Total	25.1 (1795/7145)	1.0 (3/302)	23.1 (401/1735)	5.8 (404/6931)
CL±P				
Drushel 1996	29.2 (467/1599)¶			
DeRoo 2003	22.9 (64/280)¶			
Shaw 2004	60.2 (2453/4072)¶			10.3 (419/4072)
Vallino-Napoli 2006	25.1 (299/1189)		33.8 (101/299)‖	8.5 (101/1189)
Stoll 2007	27.9 (109/390)		33.0 (36/109)‖	9.2 (36/390)
Russell 2008	37.0 (47/127)		34.0 (16/47)‖	12.6 (16/127)
Offerdal 2008	33.3 (22/66)		4.5 (1/22)	1.5 (1/66)
Beriaghi 2009	26.4 (157/595)¶			
Gillham 2009	7.2 (16/222)	0.0 (0/206)	6.3 (1/16)	0.5 (1/222)
Total	42.6 (3634/8540)	0.0 (0/206)	31.4 (155/493)	9.5 (574/6066)
CP				
Drushel 1996	43.6 (517/1187)¶			
Kallen 1996	29.0 (732/2527)		18.3 (134/732)‖	5.3 (134/2527)
Milerad 1997	22.2 (53/239)¶			
DeRoo 2003	64.9 (144/222)¶			
Shaw 2004	71.1 (1665/2343)¶			10.6 (249/2343)
Vallino-Napoli 2006	41.7 (347/833)		21.0 (73/347)‖	8.8 (73/833)
Stoll 2007	47.9 (125/261)		14.4 (18/125)‖	6.9 (18/261)
Russell 2008	53.1 (52/98)		11.5 (6/52)‖	6.1 (6/98)
Offerdal 2008	50.0 (10/20)		30.0 (3/10)	15.0 (3/20)
Tan 2009‡‡	23.1 (27/117)		29.6 (8/27)‖	6.8 (8/117)
Beriaghi 2009	38.7 (206/532)¶			
Gillham 2009	26.6 (67/252)			
Maarse 2011	52.9 (9/17)		0.0 (0/9)	0.0 (0/17)
Rittler 2011	42.3 (83/196)	0.0 (0/113)	12.0 (10/83)	5.1 (10/196)
Rozendaal 2012	78.3 (54/69)	13.3 (2/15)	16.7 (9/54)	15.9 (11/69)
Total	45.9 (4091/ 8913)	1.6 (2/128)	18.1 (261/1439)	7.9 (512/6481)

CL = cleft lip only; CLP = cleft lip with cleft palate; CL±P = cleft lip with or without cleft palate; CP = cleft palate only. Blanc entry: data were not available or could not be deducted.

* Information on karyotype not available for all clefts, unless stated differently (see Table 1). Therefore, inclusion of undetected chromosomal defects cannot be ruled out. Null values were given only if information about chromosomal analysis was reported.

† Median cleft lip and atypical facial clefts were excluded because of their different pathogenesis.

‡ Karyotype available for all clefts.

§ For one case with a chromosomal defect, data on associated anomalies were not available.

‖ Retrospective analysis of data from birth or birth defect registries. Although not specifically mentioned whether chromosomal defects were accompanied by additional anomalies, we assumed that karyotype analysis had been performed only in associated clefts (as is generally done in clinical practice).

¶ No specific data given about type of associated anomalies, including chromosomal defects. Therefore, inclusion of chromosomal defects in isolated clefts cannot be ruled out.

** Because of limited data, chromosomal defects among isolated clefts not given.

†† Including deletions 22q11.2 identified by array CGH.

‡‡ Pierre Robin sequence excluded.

They found diagnostic evidence for chromosomal defects in 1.8% (2/110) of the CL cases (both having a deletion 22q11.2), and in 1.0% (3/302) of the CLP cases. The latter three cases showed a deletion 22q11.2, a 46,X,del(X)(q1.3), and a 46,XY, add(15)(p11). As the 22q11.2 deletions were identified with array comparative genomic hybridisation (array CGH) during follow-up, the rate of chromosomal defects detected by standard karyotyping was 0% (0/110) and 0.7% (2/302) for CL and CLP, respectively. Although the rate of karyotyped cases was not known in the study of Rozendaal et al,[22] they found that two out of 15 isolated CP cases had chromosomal defects (trisomy 21 and 46,XY,add(14)(p), respectively). In both cases, the identification of the chromosomal abnormality was delayed due to the absence of additional congenital anomalies. An inventory of the reported chromosomal defects, non- chromosomal syndromes, and other diagnoses associated with prenatally and/or postnatally detected clefts is provided in supplementary table 2.

Table 2. *Summary of published prevalence data on associated anomalies and chromosomal defects in prenatally and postnatally detected unilateral and bilateral oral clefts*

Study Type	Associated Anomalies		Chromosomal Defects					
			*Isolated clefts**		*Associated clefts**		*Total clefts**	
	Unilateral % (n)	Bilateral % (n)	Unilateral % (n)	Bilateral % (n)	Unilateral % (n)	Bilateral % (n)	Unilateral % (n)	Bilateral % (n)
Prenatal studies								
CLP								
Nyberg 1995†	40.0 (6/15)	55.0 (10/20)	11.1 (1/9)	0.0 (0/10)	33.3 (2/6)	54.4 (6/10)	20.0 (3/15)	30.0 (6/20)
Berge 2001†	52.0 (13/25)	78.6 (22/28)	0.0 (0/12)	0.0 (0/6)	61.5 (8/13)	72.7 (16/22)	32.0 (8/25)	58.6 (17/29)§
Maarse 2011†	35.3 (6/17)	50.0 (3/6)	0.0 (0/11)	33.3 (1/3)	66.7 (4/6)	66.7 (2/3)	23.5 (4/17)	50.0 (3/6)
Total	45.6 (26/57)	64.8 (35/54)	4.8 (1/32)	5.3 (1/19)	57.7 (15/25)	68.6 (24/35)	26.3 (15/57)	47.3 (26/55)§
CL±P								
Perrotin 2001†	24.1 (7/29)	48.1 (13/27)	0.0 (0/22)	0.0 (0/14)	57.1 (4/7)‡	53.8 (7/13)‡	13.8 (4/29)	25.9 (7/27)
Gillham 2009†	15.5 (18/116)	22.9 (8/35)	0.0 (0/98)	0.0 (0/27)	33.3 (6/18)	37.5 (3/8)	5.2 (6/116)	8.6 (3/35)
Total	17.2 (25/145)	33.9 (21/62)	0.0 (0/110)	0.0 (0/41)	40.0 (10/25)	47.6 (10/21)	6.9 (10/145)	16.1 (10/62)
Postnatal studies								
CL								
Walker 2001‖	8.3 (6/72)	8.3 (1/12)			16.7 (1/6)	0.0 (0/1)	1.4 (1/72)	0.0 (0/12)
CLP								
Walker 2001‖	20.5 (23/112)	31.3 (21/67)			21.7 (5/23)	42.9 (9/21)	4.5 (5/112)	13.4 (9/67)

CL = cleft lip only; CLP = cleft lip with cleft palate; CL±P = cleft lip with or without cleft palate; CP = cleft palate only. Blanc entry: data were not available or could not be deducted.

* Information on karyotype not available for all clefts, unless stated differently (see Table 1). Therefore, inclusion of undetected chromosomal defects cannot be ruled out. Null values were given only if information about chromosomal analysis was reported.

† Median cleft lip and atypical facial clefts were excluded because of their different pathogenesis.

‡ Karyotype available for all clefts.

§ For one case with a chromosomal defect, data on associated anomalies were not available.

‖ Because of limited data, chromosomal defects among isolated clefts not given.

DISCUSSION

This systematic review assessed the association of prenatally and postnatally detected oral clefts with other congenital anomalies and underlying chromosomal defects, thereby providing a basis for prenatal counselling and well-informed decisions on invasive prenatal diagnostics in clefts. We demonstrated that the prevalence of associated structural and chromosomal defects is evidently related to cleft category. Although varying in study characteristics and designs, both pre- and postnatal studies showed a higher frequency of associated anomalies and chromosomal defects in CLP and CP than in CL. For all cleft categories, chromosomal defects were almost always seen in association with additional congenital anomalies. Therefore, the presence of additional anomalies on ultra- sound is the most important predictor of underlying chromosomal defects in fetuses with oral clefts.

Methodological issues

The use of both prenatal and postnatal studies—including detailed Dutch registry data—gave our study its main strength. It allowed us to provide a more reliable and representative basis for prenatal counselling and genetic testing than when only prenatal studies were evaluated. As the proportion of detected isolated clefts in prenatal populations is rising, previous prenatal studies may not have provided representative samples of current/future prenatal cleft populations. Overall, prenatal rates of associated anomalies and chromosomal defects may have been too high, because associated clefts are more likely to be detected by ultrasound than isolated clefts,[11] and some prenatal cases never reach term due to lethal anomalies or termination of pregnancy (TOP).[16 25 26 29] Another advantage of our evaluation of postnatal studies is that congenital anomalies not detected by ultrasound were also included. In particular, studies with a longer follow-up allowed us to consider minor anomalies and features that become more evident later in life.[22] For example, individuals with the velo-cardio-facial (VCF) syndrome (22q11.2 deletion) are often diagnosed at school age when speech and learning difficulties become evident, unless a cardiac defect manifests earlier.[38] Our study was also strengthened by its focus on clinical genetic aspects. If provided, karyotype information was evaluated and separate rates of chromosomal

defects among isolated (if available) and associated clefts were calculated. Besides these prevalence rates, we also composed an inventory of the different syndromes and chromosomal defects in prenatally and/or postnatally detected clefts reported by the reviewed studies and complemented with Dutch registry data, thereby specifying the detected anomalies (supplementary table 2).

However, combining results from different studies also had its limitations, mainly due to methodological issues. As summarized in supplementary table 1, we found many differences in study characteristics and designs between the reviewed studies, which are in line with those reported by Wyszynski et al.[17] The most important issue was non-uniform subdivision of oral clefts. Some studies distinguished CL and CLP, [6 7 13 25 27 28 30 31 33] while others grouped them as CL±P.[8 14–16 26 29 32 34–36] Together with previous studies,[2–5] our results stress the need of accurate prenatal subdivision into three categories (CL, CLP, and CP). Obviously, analysing CL and CLP as one group will result in different frequencies of associated anomalies and chromosomal defects than when they are analysed separately. Unfortunately, prenatal distinction between CL and CLP can be limited because prenatal identification of involvement of the palate is still challenging.[11 14] For this reason, data on prenatally detected CP were limited in the current study. However, there is evidence of improvements in imaging, as well as in experience in detection and interpretation of subtle signs on ultrasound,[39 40] which will progressively reduce the lower limits for detection.

Another important factor was that associated anomalies were differently defined and classified in the evaluated studies, which partly explains the wide variation in the reported rates of associated anomalies.[17] The definitions in the reviewed studies ranged from only major (structural) non-facial congenital anomalies to all anomalies, including minor congenital anomalies and ultrasound markers, such as intrauterine growth retardation (supplementary table 1). This might explain, at least partially, the relatively high rates of associated anomalies reported by Rozendaal et al,[22] who also included minor and dysmorphic features in their analysis. Although these minimal defects are hardly detected prenatally, they may be recognisable components of specific syndromes or chromosomal defects in postnatally detected clefts.[17] Similarly, the high prevalence reported by Shaw et al[35] could also partly be due to the inclusion of minor defects, as they used diagnostic codes with low specificity, including the

malformation groups 'ear, face, neck' and 'upper alimentary tract'. Another source of variation is the inconsistent definition of the Robin sequence applied in clinical practice and consequently its over- or under-reporting.[41] Some of the reviewed studies classified this condition—CP combined with micrognathia, glossoptosis and airway compromise—as isolated CP,[26 27 33] while other studies considered it as a separate category[28 31] or as associated CP.[11 14 16 22 29]

The reviewed studies also varied considerably in their reporting of karyotypic information (supplementary table 1). While some studies provided explicit information about the number of karyotyped cases and their detected associated and chromosomal defects,[6–8 13–15 22 25 27] others reported only abnormal karyotypes, but not their associated anomalies,[16 26 28–31] or they did not give any specific data at all.[32–36] As a consequence, separate and complete rates of chromosomal defects could not always be obtained. Furthermore, in studies providing explicit information, chromosomal analysis was mostly performed in associated clefts only, which explains why almost all reported chromosomal defects were accompanied by additional anomalies. It is important to realise that most of these studies obtained chromosome results for just a part—and not all—of the clefts, and that the inclusion of cases with undetected chromosomal defects in their rates therefore cannot be ruled out. Besides karyotype analysis, most studies also did not report whether FISH analysis had been performed and whether microdeletions were included in the presented data. Only the studies of Tan et al,[31] Rittler et al,[27] and Rozendaal et al[22] reported the inclusion of microdeletions or duplications, while Stoll et al[26] included the results of FISH22q11 screening as from 1994. In contrast, Kallen et al[28] reported not to have included microdeletions, which might have led to an underestimation of the frequency of underlying chromosomal defects. On the other hand, some studies may have overrepresented chromosomal defects in association with oral clefts due to the inclusion of sex chromosome abnormalities. For example, Stoll et al[26] showed that 12 out of 54 abnormal karyotypes concerned abnormalities of sex chromosomes, which may be coincidental findings and not related to clefts. From the literature, no convincing evidence is provided that the most frequently detected sex chromosomal anomalies (eg, 47, XXX; and 47, XXY) are actually related to clefts.

Differences in study settings and data sources between studies (supplementary table 1) may also have accounted for the variation in the prevalence of associated anomalies

and are possible sources of selection bias. For example, some studies were performed with data from prenatal centres,[6–8 13 15] while others were retrospectively conducted via the so-called 'cleft palate teams'.[14 16] Consequently, the retrospective cleft team studies did not include the fetuses that were not born alive and were thus not referred to the cleft palate teams, thereby inducing selection bias. Additionally, according to Wyszynski et al,[17] information obtained from vital records (eg, birth certificates) is neither complete nor accurate in detail due to passive ascertainment methods (ie, data submitted by data sources and not actively collected by registry staff searching data sources for eligible cases) and lack of follow-up. Conversely, studies having active ascertainment methods or long follow-up periods, such as that of Rozendaal et al (median follow-up 5 years),[22] may result in relatively high rates of associated anomalies. Also, the value of information depends on the interest and skills of the person who records the anomalies. This is in line with the study of Tan et al,[31] who reported higher frequencies of associated anomalies in patients recruited for a clinical study than in cases derived from a birth defect register. They suggested this was explained by a combination of ascertainment bias and more complete diagnosis by detailed clinical assessment in the clinical study. Nevertheless, despite the above mentioned issues, we found unambiguous evidence that the three cleft categories are differently associated with structural and chromosomal defects. Due to the inclusion of large numbers of cases from both prenatal and postnatal populations, we were able to provide a rather reliable basis for clinicians and future parents, thereby allowing accurate counselling and informed decisions on whether to have invasive diagnostics if an oral cleft is detected prenatally.

Prenatal counselling and genetic testing

When counselling future parents regarding prognosis and risk of associated chromosomal defects, it is vital to tailor the discussion according to cleft category. As our results showed, CLP and CP are more frequently associated with additional anomalies and chromosomal defects than CL. Moreover, these frequencies are higher in bilateral than in unilateral CLP or CL±P. This emphasises the need for accurate prenatal subdivision of clefts. However, accurate detection of additional anomalies appears to be even more significant to outcome. As we found, the presence of other congenital

anomalies is a strong predictor for chromosomal defects. For all cleft categories, both prenatal and postnatal studies showed that chromosomal abnormalities are almost always seen in association with other congenital anomalies. Therefore, invasive prenatal testing to identify chromosomal abnormalities in combination with genetic counselling should be offered in all cases with associated anomalies, irrespective of cleft category. It should be realised, however, that the absence of associated anomalies does not exclude the possibility of the presence of an underlying chromosomal defect. As mentioned above, chromosomal analysis was often not performed in isolated cases, and therefore undetected chromosomal defects might have been included in our rates of isolated clefts. The few studies that reported chromosomal defects in isolated clefts showed that the prevalence differed by category. As standard karyotyping did not reveal any chromosomal defect, cases with isolated CL have the most favourable prognosis when it comes to chromosomal anomalies with a poor outcome. Therefore, if confident in ultrasound findings, conventional karyotyping is not recommended in isolated CL. However, based on the findings of Rittler et al,[27] array CGH to detect deletion 22q11.2 should be considered.

For CLP, prenatal studies together showed chromosomal defects in 3.9% of the presumed isolated cases, while just one postnatal study addressed this issue showing defects in 1.0%. In the latter study,[27] standard karyotyping revealed chromosomal defects in 0.7% of the isolated CLP cases, while array CGH during follow-up revealed a deletion 22q11.2 for one more case. Based on these data, it is recommended to inform future parents about the possible association of a chromosomal defect and to consider invasive prenatal testing in these cases, preferably by array based methods. However, if not confident in ultrasound findings regarding cleft category, it should be noted that the overall prevalence in presumed isolated clefts (CP excluded) was 0.8% (7/830). Furthermore, when considering invasive testing, the baseline risk of complications (1%) should be weighed against the potential benefits.[42] Another concern might be the detection of unexpected or unclassified variants with array based methods, which should be discussed with future parents.

Regarding CP, especially isolated CP, prenatal identification is still challenging, which has resulted in limited prenatal information on their underlying chromosomal defects.

However, postnatal karyotyping of isolated CP cases revealed a chromosomal defect in 1.6%. In this category in particular, specific syndromes, such as VCF (22q11.2 deletion), Treacher-Collins, and Stickler, have to be considered. As presented in supplementary table 2, these syndrome diagnoses were frequently reported in the evaluated literature. Therefore, until more information on chromosomal defects in prenatally presumed isolated CP is available, we advise consideration of invasive genetic testing and consultation by a clinical geneticist if an isolated CP is detected prenatally. A prenatal diagnostic algorithm according to cleft category is presented in figure 1.

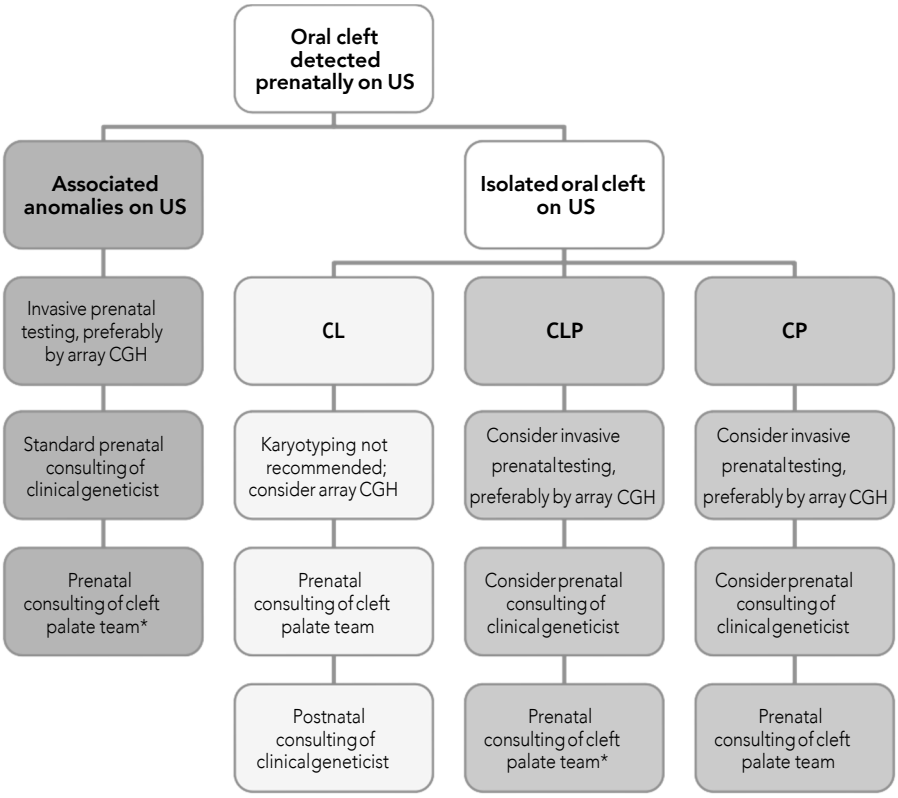

Figure 1. *Algorithm for invasive genetic testing according to oral cleft category. CL = cleft lip only; CLP = cleft lip with cleft palate; CP = cleft palate only; US = ultrasound; array CGH = array-comparative genomic hybridization. * If a normal karyotype is confirmed or invasive genetic testing is declined.*

Based on the above findings, more accurate prenatal ultrasound screening will improve counselling, especially regarding palatal involvement. Therefore, we advise the referral of pregnant women with a fetus suspected of having an oral cleft to a tertiary care centre where more specific ultrasound screening can be performed. In addition, if a normal karyotype is confirmed or invasive testing is declined, future parents should be counselled by a multidisciplinary cleft palate team that focuses on psychosocial support, education on management of clefts, and parents' options, TOP being one of them.[43–46] Finally, it is crucial to distinguish median clefts and atypical facial clefts from oral clefts. These different craniofacial anomalies are associated with other congenital anomalies and have a different prognosis, and should therefore be referred to and treated by specialised multidisciplinary craniofacial teams.

Future studies

The use of array CGH in clinical practice is rising, and it is expected that it will be implemented as standard prenatal diagnostics in the near future. Compared to conventional karyotyping, array CGH can detect smaller chromosome deletions and duplications. To gain more insight into the yield of array CGH in cases with clefts, it would be interesting to perform array CGH in a large cohort of cases with prenatally and postnatally detected clefts. This would also give us more information about the proportion and types of chromosomal defects that are missed in cases that have not been karyotyped or studied by array based methods. Particularly with regard to prenatally presumed isolated clefts, this is essential to reach consensus on the role of invasive genetic testing in these cases. As was demonstrated by the NVSCA data,[23 24] clefts can be associated with various microdeletions and duplications. This implies that array CGH should be the standard technique to identify chromosomal defects in children with oral clefts.

Finally, follow-up studies are needed to gain more insight into additional abnormalities and chromosomal anomalies identified after birth. This can aid in more optimal counselling of future parents, especially with regard to unexpected anomalies in presumed isolated clefts, and timely treatment of children with clefts.

CONCLUSIONS

This systematic review presents unambiguous evidence that the different cleft categories are variously associated with additional congenital anomalies and underlying chromosomal defects. This emphasises the need for accurate subdivision of CL, CLP and CP for both ultrasound screening and postnatal follow-up. However, the most important predictor of chromosomal abnormalities is the presence of associated anomalies, and we urge clinicians to advise invasive testing in these cases. In the absence of associated anomalies, cases with CL have the most favourable prognosis and do not require conventional karyotyping. In presumed isolated CLP and CP, professionals should explain the possible association of a chromosomal defect and consider invasive genetic testing, preferably by array based methods. In all cleft categories, an association with deletion 22q11.2 should be considered.
Accurate prenatal diagnosis by ultrasound is essential in the quality of counselling, especially with regard to palatal involvement and associated anomalies. Therefore, a pregnant woman with a fetus suspected of having an oral cleft should be referred to a tertiary care centre where more specific ultrasound screening can be performed. Finally, follow-up studies, including array CGH, are needed to gain more insight into additional abnormalities and chromosomal defects missed in associated and presumed isolated clefts. This would aid in more optimal counselling and timely treatment of children with oral clefts.

ACKNOWLEDGEMENTS

The authors would like to thank the clinical cytogeneticist Ellen van Binsbergen for her cytogenetic input as well as the clinical cytogeneticist Heleen Schuring-Blom and psychologist Henriëtte Swanenburg de Veye for their helpful discussion and critically reading of the manuscript. They would also like to express their gratitude to the Dutch cleft palate teams and the NVSCA, including its board. Without their efforts, the NVSCA would not have succeeded.

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Supplementary Table 1 Summary of the various study characteristics and designs of the prenatal and postnatal studies included in the systematic review

Study type	Study area	Study population and setting	Inclusion criteria	Data sources and collection	Definition & classification associated congenital anomalies	Karyotype information
Prenatal studies						
Nyberg 1995	Not given	High-risk obstetric cases referred to tertiary referral centres 1988-1993*	Live births, stillbirths, and TOP with oral clefts *(n=40)*†	Prospective and retrospective analysis of sonograms & postnatal information retrieved by inspection at autopsy or after birth	Major and minor congenital anomalies; IUGR and other ultrasound markers‡	Karyotype given for most associated clefts (94%, 17/18); number of isolated clefts karyotyped not given
Berge 2001	Region of Bonn, Germany	High-risk obstetric cases referred to a single tertiary referral centre 1991-2000*	Live births, stillbirths, and TOP with oral clefts *(n=59)*†	Prospective and retrospective analysis of sonograms & postnatal follow-up data from neonatologist and surgeons, and pathological and cytogenetic records	Major and minor congenital anomalies; IUGR and other ultrasound markers‡	Karyotype given for most associated clefts (94%, 33/35) and isolated clefts (76%, 16/21)
Perrotin 2001	Region of Tours, France	High-risk obstetric cases referred to a single tertiary referral centre 1991-1999*	Live births, stillbirths, and TOP with oral clefts *(n=56)*†	Retrospective evaluation of ultrasonographic and clinical records, and ascertainment via autopsy reports or hospital records with a postnatal follow-up of 3-12 months	Major and minor congenital anomalies; IUGR and other ultrasound markers	Karyotype given for all associated clefts (n=20), and some isolated clefts (39%, 14/36)
Prenatal and Postnatal studies						
Offerdal 2008	Region of Trondheim, Norway	Pregnant women in a non-selected population who underwent routine ultrasound examination 1987-2004 *(n=49,314)*	Live births, stillbirths, and TOP (≥16 weeks gestation) with oral clefts *(n=101)*	Prospective collection of ultrasound examinations & prenatal and postnatal follow-up data from autopsy reports, photographs, physical examinations by paediatricians and review of medical records	Structural congenital anomalies, sequences, and non-chromosomal syndromes according to the ICD; Additional anomalies further subdivided into: - chromosome aberrations - syndromes/sequences with normal chromosomes - structural anomalies without chromosomal aberrations, syndromes or sequences	Some clefts (31%, 31/101 were karyotyped; presence/ absence of abnormal karyotype given for most associated clefts 62%, 29/47); no specific data given
Russell 2008	Novia Scotia, Canada	Births to residents of Novia Scotia registered in the Perinatal Database, Fetal Anomaly Database, or Cleft Palate Database 1992-2002 *(n=108,220)*	Live births, stillbirths, and TOP with oral clefts *(n=225)*	Data from the population-based Novia Scotia Atlee Perinatal Database, the Fetal Anomaly Database, and Cleft Palate Database	Structural congenital anomalies; Additional anomalies further subdivided into: - with abnormal karyotype - structural/syndromic with normal karyotype	Data suggest that all associated clefts (n=99) were karyotyped; no specific data given

Gillham 2009	North-West England	Obstetric cases prenatally suspected of an oral cleft and referred to the Regional Fetal Management Unit & infants referred to the regional cleft team 2000-2006 *(n=570)*	Live births, stillbirths, and TOP with oral clefts *(n=490)*†	Retrospective review of prenatal diagnoses in the North-West Regional Fetal Management Unit Database & postnatal findings in the North-West Cleft Lip and Palate Database	Structural congenital anomalies	Almost all associated clefts (97%, 29/30) were karyotyped; all isolated clefts were karyotyped
Maarse 2011	Region of Utrecht, Netherlands	Pregnant women in a non-selected population who underwent routine ultrasound examination 2007-2008, including low-risk (n= 35,924) and high-risk cases *(n=2,836)*	Live births, stillbirths, and TOP with oral clefts *(n=60)*†	Retrospective evaluation of ultrasound examinations from prenatal screening centres and clinical records of the cleft palate team	Major and minor congenital anomalies; IUGR and other ultrasound markers (20 weeks gestation); abnormal karyotype defined as associated anomaly	Some clefts were karyotyped; total number of associated and isolated clefts karyotyped not given
Postnatal studies						
Druschel 1996	New York State, USA	Children born to New York residents, registered with an oral cleft before the age of 2 years in the Congenital Malformation Registry, and matched to their birth certificate 1983-1990 *(n=2,786)*	Live births with oral clefts *(n=2,786)*	Retrospective review of data from the population-based database of New York State Congenital Malformations Registry and from additional registry sources, including birth certificates	Major congenital anomalies, and minor congenital anomalies (only if they were associated with major anomalies)	No information given
Kallen 1996	Central-East of France/ Sweden/ California, USA	Births registered to 3 registries of the International Clearinghouse for Birth Monitoring Systems: France, 1976-1992 *(n= 1.46 million)*; Sweden, 1973-1992 *(n=2.07 million)*; California, 1983-1990 *(n=1.62 million)*	Live births and stillbirths (≥28 weeks gestation) with oral clefts *(n=8,315)*	Data from the population-based databases of Central-East France, National Sweden's Registry, and the California Birth Defects Monitoring Program; malformations were retrospectively ascertained up to an age of one year	Major non-facial congenital structural anomalies	Identified karyotypes presented; number of associated and isolated clefts karyotyped not given
Milerad 1997	Region of Stockholm, Sweden	Children with oral clefts referred to the regional cleft palate team of Stockholm or reported to the National Malformation Registry 1975-1992 *(n=616)*	Live births with oral clefts (*n=616*; submucous CP excluded)	Retrospective review of cleft palate team files, and birth and hospital records	Congenital anomalies that require follow-up or intervention; Abnormal karyotype defined as associated anomaly	Most identified karyotypes (94%, 16/17) presented; not classified according cleft category

Walker 2001	Utah, USA	Births to residents of the statewide non-selected non-referred population of Utah 1995-1999 *(n=217,429)*	Live births, stillbirths, and TOP with CL or CLP (*n=263*; CP only excluded)	Data from the Utah Department of Health Birth Defect Network population-based surveillance system	Major anatomic congenital anomalies (that is, those anomalies that would alter pregnancy management or result in functional impairment of the child)	Most associated clefts (75%, 38/51), and few isolated clefts (0.6%, 12/212) were karyotyped
DeRoo 2003	Washington State, USA	Live-born infants to residents of the statewide population of Washington 1987-1990 *(n=298,138)*	Live births with oral clefts *(n=608)*	Data from the Washington State Birth Defects Registry population-based surveillance system on congenital anomalies diagnosed within the first year of life & Washington State birth certificates	Major congenital anomalies, confirmed genetic anomalies and recognized syndromes	No information given
Shaw 2004	California, USA	Deliveries (≥20 weeks gestation) to California women in non-military hospitals 1983-1997 *(n=3,572,230)*	Live births, stillbirths, and TOP (≥20 weeks gestation) with oral clefts *(n=6,415)*	Data from the California Birth Defects Monitoring Program, population-based active surveillance system on congenital anomalies diagnosed within 1 year of delivery	Structural congenital anomalies according to the BPA; Abnormal karyotype defined as associated anomaly	No information given
Vallino-Napoli 2006	Victoria, Australia	Pregnancies in Victoria 1983-2000 *(n=1,140,668)*	Live births, stillbirths, and TOP (<20 weeks gestation) with oral clefts *(n=2,022)*	Data from the population-based Victorian Birth Defects Registry	Major congenital anomalies, PRS, chromosomal anomalies, and non-chromosomal syndromes	Some clefts karyotyped; number of associated and isolated clefts karyotyped not given
Calzolari 2007	Europe	Births registered to 23 registers in 14 European countries 1980-2000 *(n=5,989,834)*	Live births, stillbirths, and TOP with CL or CLP *(n=5,449)*	Data from the European network (EUROCAT) of 23 registers in 14 European countries, having various periods of follow-up	Two or more unrelated congenital anomalies according to the BPA; Additional anomalies further subdivided into: - recognized conditions (including chromosomal) - MCA	Some clefts were karyotyped; number of associated and isolated clefts karyotyped not given
Stoll 2007	Region of Strasbourg, France	Newborns and foetuses delivered in 11 maternity hospitals in Strasbourg and surrounding rural areas 1979-2003 (*n=334,262*; no home deliveries in this area)	Live births, stillbirths, and TOP with oral clefts (n=651; submucous CP excluded)	Data from the regional registry of congenital malformation on anomalies diagnosed within 1 year of age	One or more non-cleft major congenital anomalies§; Additional anomalies further subdivided into: - chromosomal - non-chromosomal	All associated clefts were karyotyped

Beriaghi 2009	Omaha, Nebraska, USA	Children with oral clefts referred to the cleft palate/craniofacial clinic 1980-2000 *(n=1,127)*	Live births with oral clefts *(n=1,127)*	Data from the craniofacial centre database obtained by the multidisciplinary team	Congenital anomalies (slight variations of normal & neurological and behavioural abnormalities excluded); Abnormal karyotype defined as associated anomaly	No information given
Tan 2009	Victoria, Australia	Children born in Victoria and registered with an oral cleft in the Birth Defects Register 2000-2002 (n=312)	Live births with oral clefts (n=279)‖	Data from the Victorian Birth Defects Register on congenital anomalies diagnosed within 15 years of age	Structural, functional, genetic, chromosomal, and biochemical abnormalities after birth	Some clefts were karyotyped; number of associated and isolated clefts karyotyped not given
Rittler 2011	South America	Children with congenital anomalies ascertained at birth in 48 maternity hospitals from 7 countries of the ECLAMC network, within the framework of a special intervention study 2003-2005 (n=10,371)¶	Live births with oral clefts (*n=710*; those with a bifid uvula, congenitally 'healed' CL, submucous CP, or birth weight < 500 g excluded)	Information reported by paediatricians and retrieved by further evaluation by dysmorphologists and geneticists during a follow-up period of 1 year	Major unrelated defects (that is, those requiring medical or surgical intervention, or of substantial cosmetic importance, and clinically recognizable or suspected syndromes) detected and reported between birth and hospital discharge; PRS was classified as isolated CP; Additional anomalies further subdivided into: - chromosomal anomaly - syndromes without chromosomal anomalies - malformation complexes/sequences - MCA	All clefts were karyotyped; information available for most associated (58%, 108/185) and isolated clefts (54%, 281/525); FISH 22q11 was not regularly performed; array CGH was performed in some clefts
Rozendaal 2011	Netherlands	Children with oral clefts referred to the 15 Dutch cleft palate teams in the Netherlands	Live births with oral clefts	Registry data from the National Oral Cleft Database and review of medical records (including colour photographs, X-rays, and dental casts) after a median follow-up period of 5 years	Major and minor congenital anomalies, including dysmorphic features	Some associated and isolated clefts karyotyped; number not given

TOP, termination of pregnancy; CL, cleft lip only; CLP, cleft lip with cleft palate; CP, cleft palate only; IUCR, intrauterine growth retardation; MCA, multiple congenital anomalies; PRS, Pierre Robin Sequence; EUROCAT, European Registry of Congenital Anomalies and Twins; ECLAM, Latin American Collaborative Study of Congenital Malformations; ICD, International Classification of Diseases (9th and 10th revision); BPA, malformation codes of the British Pediatric Association.

* Number of cases not given.

† Median cleft lip and/or atypical facial clefts analysed, but excluded from this review.

‡ Other ultrasound markers: e.g., oligohydramnios, polyhdyramnios, single umbilical artery, or nuchal oedema.

§ Stoll et al. excluded mental retardation and classified Pierre Robin sequence as isolated CP when it was present without congenital anomalies beyond micrognathia and glossoptosis.

|| Cases with PRS (n=33) analysed, but excluded from this review because of the inconsistent definition applied in clinical practice and consequently its over- or underreporting.

¶ Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, and Venezuela (total live births in this area: n=422,240).

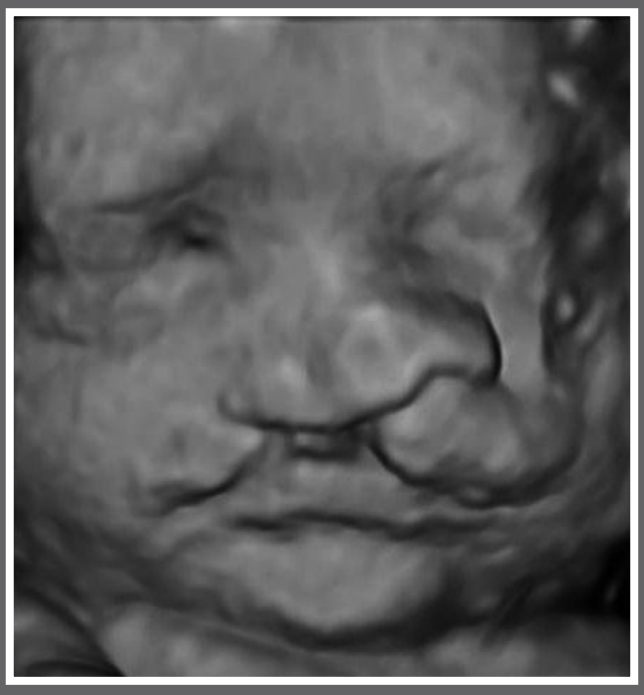
Supplementary Table 2 *Observed chromosomal defects and non-chromosomal syndromes associated with oral clefts in prenatal and/or postnatal populations*

	Studies Prenatal			Prenatal-Postnatal			Postnatal						
	Nyberg 1995	Berge 2001	Perrotin 2001	Maarse 2010	Russell 2008	Gillham 2009	Kallen 1996	Milerad 1997	Stoll 2007	Vallino 2006	Walker 2001	Rittler 2011	NVSCA 1997-2010*
Chromosomal defect													
Trisomy 6											X		
Trisomy 9p				X									
Trisomy 13	X	X	X	X	X	X		X	X	X	X	X	X
Trisomy 16p													X
Trisomy 18	X	X	X	X	X	X		X	X	X	X	X	X
Trisomy 21				X				X	X	X		X	X
Trisomy 22								X					
Triploidy 69		X											
Monosomy 21								X					
Mosaic trisomy 22	X												
Mosaic tetrasomy 12p												X	
Partial autosomal trisomy	X								X				
Translocation			X		X								
Deletion 2q								X					
Deletion 4p			X									X	X
Deletion 4q								X					
Deletion 5p14.3p14.1													X
Deletion 5q21.1q23.3													X
Deletion 13q											X		X
Deletion 22q11.2									X			X	X
46,XY,der(3)del(p26)inv dup(3)(p24p25)													X
46,XX, der(6)t(2;6)(q37;q27)pat													X
dup(11)(p11.1p15.5)pat													X
46,XY,der(14)t(14;16)(p11;p12.3)													X
46,XY,add(15)(p11)												X	
46,XX,del(16)(q22.3q22.3)													X
46,XY,der(18)t(16;18)(q24;q23)pat													X
46,XY,del(18)(q21.3)													X
47,XX,+inv dup (22)(q11q11)													X
dup(22)(q11q11)													X
Partial autosomal deletion	X								X				X
Sex chromosomal abnormalities	X							X	X			X	X
Other chromosomal abnormalities		X								X			

	Studies Prenatal			Prenatal-Postnatal			Postnatal						
	Nyberg 1995	Berge 2001	Perrotin 2001	Maarse 2010	Russell 2008	Gillham 2009	Kallen 1996	Milerad 1997	Stoll 2007	Vallino 2006	Walker 2001	Rittler 2011	NVSCA 1997-2010*
Non-chromosomal syndrome													
Adams-Oliver syndrome									X				
Amniotic band association	X									X			
Anti-epileptic drugs							X						
Apert syndrome						X	X	X					X
Beckwith-Wiedeman syndrome				X				X					X
Branchio-oculo-facial syndrome													X
Bohring-Opitz syndrome													X
Caudal Regression syndrome					X								
CHARGE syndrome						X						X	X
Chondrodystrophy							X						
Cornelia de Lange syndrome							X		X			X	X
Crouzon syndrome								X					X
DiGeorge syndrome					X					X			
Duane retraction syndrome													X
Ectrodactyly-ectodermal dysplasia-clefting syndrome							X		X				X
Encephalocele-clefting syndrome								X					
Foetal alcohol syndrome							X						
Fraser syndrome													X
Fryns syndrome			X										
Goldenhar syndrome				X			X		X	X			X
Gordon syndrome													X
Gorlin syndrome													X
Greig syndrome													X
Hay-Wells (AEC) syndrome													X
Holoprosencephaly										X			
Ivemark syndrome									X				
Jeune syndrome													X
Kabuki syndrome													
Kartagener syndrome†								X					
Klippel-Feil syndrome							X		X				X
Larsen syndrome								X				X	
Loeys-Dietz syndrome													X
Meckel-Gruber syndrome					X								
Meckel syndrome							X		X				

	Studies Prenatal			Prenatal-Postnatal			Postnatal						
	Nyberg 1995	Berge 2001	Perrotin 2001	Maarse 2010	Russell 2008	Gillham 2009	Kallen 1996	Milerad 1997	Stoll 2007	Vallino 2006	Walker 2001	Rittler 2011	NVSCA 1997-2010*
Moebius syndrome							X		X				X
Mohr syndrome												X	
Multiple epifysial dysplasia†										X			
Multiple pterygium syndrome									X				
Nager syndrome							X						X
Noonan syndrome													X
Omenn reticuloendotheliosis†									X				
Opitz-Frias syndrome			X										
Opitz G/BBB												X	X
Oro-facio-digital syndrome							X		X				X
Osler-Weber syndrome†								X					
Osteogenesis imperfecta†							X						
Osteopathia striata with cranial sclerosis													X
Oto-palato-digital syndrome	X								X				X
Pentalogy of Cantrell (Thoraco-abdominal syndrome)													X
Poland syndrome†								X					
Popliteal pterygium syndrome			X				X						
Rieger syndrome													X
Roberts syndrome									X				
Robinow syndrome								X					
Rubinstein-Taybi syndrome†											X	X	X
Smith-Lemli-Opitz syndrome					X		X	X					X
Stickler syndrome				X		X	X	X	X			X	X
Treacher-Collins syndrome							X	X	X	X			X
VACTERL													X
Van der Woude syndrome				X	X			X			X	X	X
VATER association									X				
VCF syndrome§									X				
X-linked hydrocephalus†										X			
Other diagnosis													
Neonatal Abstinence syndrome													X
Pierre Robin sequence				X	X	X			X	X			X
Sebaceus Nevus syndrome													X

* Annual reports 1997-2010 of the Dutch Association for Cleft Palate and Craniofacial anomalies, comprising data without follow-up.
† Diagnosis uncertain.
§ Clinical diagnosis, not confirmed by karyotype.



Part III
Prenatal Counseling

8

Professional opinion on oral cleft during pregnancy: a comparison between Israel and the Netherlands

Prenatal Diagnosis, 2015 Jun;35(6):544-8

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ABSTRACT

Objective To assess the opinion of obstetric care providers who perform prenatal ultrasounds to screen for anomalies and who advise women about their options, including termination of pregnancy, when an oral cleft is detected. We compared providers' opinions about pregnancy termination for isolated oral cleft in the Netherlands, where the number of terminations is low, and in Israel, where the number is high.

Methods Online questionnaires were used. The questions assessed the providers' views regarding the estimated burden of treatment, the functioning ability and the level of happiness of children with an oral cleft and their parents. Additionally, we assessed providers' opinions on pregnancy termination for isolated oral cleft.

Results In the Netherlands, more professionals considered oral cleft a disability [rate differences (RD) 17.8%, 95% CI: 0.5-33.1%] than in Israel. In the Netherlands, 10.6% of respondents (compared with 11.1% in Israel) thought that an isolated cleft was a reason for TOP [RD 0.6%, 95% CI: -12-10.9%].

Conclusions Prenatal care providers in the Netherlands and Israel do not differ in their opinions about the severity of oral cleft and the acceptability of TOP for an isolated oral cleft. This study shows that prenatal care providers' attitudes do therefore not explain the dramatic difference between these countries in the number of TOP for isolated oral cleft.

INTRODUCTION

Oral clefts are among the most common congenital malformations; they occur in approximately 1 out of 700 live births[1]. Because the use of ultrasound screening during pregnancy has become the standard of care, the prenatal diagnosis of oral clefts is common and has a detection rate of 88%[2].

There is some controversy about the parental, social and ethical consequences of prenatal detection of oral clefts[3]. The prenatal detection of an oral cleft has numerous advantages. Not only are the parents better prepared psychologically for the anomaly, but awareness of the diagnosis provides an opportunity to provide education about both the treatment of oral clefts and the management of possible feeding problems. The prenatal diagnosis of an oral cleft also provides an opportunity to offer additional genetic testing to screen for possible associated anomalies and chromosomal defects[4,5]. The disadvantages of the prenatal diagnosis of oral cleft are the possibility of a false positive diagnosis and the resulting emotional stress on the pregnancy[6,7]. The fact that at present time prenatal surgery may not be an option or may carry very high risks is another disadvantage[8]. Additionally there are concerns about the possible increasing number of terminations of pregnancy (TOP) of fetuses with an isolated oral cleft[9]. Because most nonsyndromic oral clefts are nonlethal birth defects that have an excellent functional and aesthetic prognosis with proper treatment, the use of prenatal diagnosis raises important ethical issues, especially in terms of TOP[10,11].

High numbers of TOPs for prenatally diagnosed isolated oral clefts have been reported in Israel (93.4%)[9]. In the Netherlands, the number of parents who choose TOP when an oral cleft is detected is low (6.7%)[12]. The reasons for these differences are unknown. In addition to cultural and religious influences, the perception of burden and the stigma of having a 'less-than-perfect' child may be significant contributing factors[13]. Caregivers who counsel future parents could be another influencing factor[14]. Little is known about prenatal care providers' attitudes towards various conditions for which prenatal diagnosis is available. The goal of the present study was to assess the opinions about oral clefts and TOP among obstetric care providers in Israel and the Netherlands. Specifically, we sought to determine whether personal attitudes were

a plausible explanation for the large difference in TOPs for isolated cleft in these countries.

METHODS

A cross-sectional quantitative study was performed. In the Netherlands, routine screening two-dimensional (2D) ultrasound is offered to all pregnant women at approximately 20 weeks of gestation. In Israel, a first screening is offered earlier, between 14 and 16 weeks of gestation.
In August 2013, an online questionnaire was distributed digitally in the Netherlands (Dutch) and Israel (Hebrew) to all obstetric care providers who perform prenatal ultrasounds. In the Netherlands, we approached a subgroup of the Dutch Society of Obstetrics and Gynecology composed only of gynecologists and midwives who specialize in prenatal care. In the Netherlands, trained midwives, sonographers and gynecologists perform routine 2D ultrasound screening in several centers. If an abnormality is suspected, the pregnant woman is referred to a specialized center, where certified gynecologists perform more extensive two-, and three-dimensional ultrasound examinations and provide counseling. In Israel, the questionnaire was sent to all gynecologists through the Israeli Society of Obstetrics and Gynecology. Unlike in the Netherlands, there is no subgroup of gynecologists in Israel who specialize in prenatal care.
In both countries, gynecologists offer future parents a referral to a cleft team for additional prenatal counseling when an oral cleft is diagnosed prenatally. However, the parents ultimately decide whether to take advantage of this opportunity.

The questionnaire used in this study was derived from one previously published by Korenromp et al.[15], who explored decision-making processes regarding TOP for Down syndrome. The questionnaire was translated into Hebrew (in a back-and-forward manner) by two of the authors (O.L. and M.K).
In the questionnaire, obstetric care providers were asked about their perception of the estimated severity of an oral cleft (by means of whether they would describe a cleft as

a 'trait', a 'little different from normal', a 'cosmetic defect', a 'disability', a 'disorder' or a 'disease') and whether they believed that an oral cleft was a reason for a TOP. To place this question in perspective, the care providers were also asked for their opinion regarding other reasons for TOP (Table 1). Additionally, care providers were asked their opinion about the estimated treatment burden for the child and the parents (on a scale of 0-100, where 0 was 'not serious' and 100 was 'very serious') and the influence of the oral cleft on the parent's and child's happiness and ability to function (on a scale from 0-100, where 0 was 'not seriously influenced' and 100 was 'very serious influenced'; Table 2).

Statistical analysis was performed using SPSS statistical software (version 20.0) and Rothman's Episheet (11 June 2008). We used the rate (percentage) or mean differences with corresponding 95% confidence intervals (CIs) to compare the Dutch and Israeli results.

RESULTS

In the Netherlands, the response rate was 42.8% (142/332), and the questionnaire was completed by 92 (64.8%) gynecologists, 19 (13.4%) midwives, 19 (13.4%) ultrasonographers and 12 (8.4%) other professionals, such as a pediatricians or medical geneticists. In Israel, all of the respondents were gynecologists (n=41). The exact number of Israeli gynecologists who perform prenatal ultrasounds is not known; however, another survey study from Israel[17] estimated that 100 gynecologists perform this service. Thus, the response rate was similar. In the Netherlands, more professionals had diagnosed an oral cleft in their professional careers: 88% compared with 72.5% in Israel [rate difference (RD) 15.5%, 95% CI: 0.7-30.4%].

The oral cleft descriptions that the respondents used are outlined in Table 1. None of the respondents defined an oral cleft as a trait similar to hair color. In both countries, 'disability' was the most frequent answer, though the percentage was higher in the Netherlands (60.3%) compared with Israel [42.5%; RD 17.8%, 95% CI: 0.5-33.1%]. Thirty-five percent of the Israeli professionals classified an oral cleft as a cosmetic defect, whereas 20.6% of the respondents in the Netherlands used that classification [RD -14.4%, 95 CI:-30.7-1.8%].

There was no difference in the percentage of professionals in the Netherlands (10.6%) and in Israel (11.1%) who thought that an isolated cleft was a reason for TOP [RD 0.6%, 95% CI: -12- to 10.9%]. However, there were significant differences in the circumstances under which professionals considered TOP an option (a positive RD indicated that the percentage in the Netherlands was higher, and a negative RD indicated that the percentage in Israel was higher). These circumstances included Down syndrome [RD 15.9%, 95% CI: 0.9 to 30.9%], spina bifida [RD 28.8%, 95% CI: 13.5 to 44.2%], wheelchair dependency [RD -20%, 95% CI: -36.2 to -3.9%] and diseases that would occur later in life [RD 22.6%, 95% CI: 10.7 to 34.5%].

Table 1 *Professional opinions about oral cleft*

Question	The Netherlands (N = 142) N (%)	Israel (N = 41) N (%)	Rate differences (95% CI)
How would you define oral cleft?			
Small difference from normal	5 (3.5%)	3 (7.5%)	-4% (-12.7 to 4.8%)
Cosmetic defect	29 (20.6%)	14 (35.0%)	-14.4% (-30.7 to 1.8%)
Disability	85 (60.3%)	17 (42.5%)	**17.8%** (0.5 to 35.1%)
Disorder	3 (2.1%)	3 (7.5%)	-5.4% (-13.9 to 3.1%)
Disease	0 (0.0%)	1 (2.5%)	-2.5% (-7.3 to 3.2%)
Do you think isolated oral cleft is a reason for TOP?			
Yes	15 (10.6%)	4 (11.1%)	-0.6% (-12 to 10.9%)
Are there circumstances in which TOP could be an option?			
Down syndrome	123 (86.6%)	29 (70.7%)	**15.9%** (0.9 to 30.9%)
Spina bifida	131 (92.3%)	26 (63.4%)	**28.8%** (13.5 to 44.2%)
Other mental handicap or disorder	108(76.1%)	30 (73.2%)	2.9% (-12.4 to 18.2%)
Wheelchair dependency	72 (50.7%)	29 (70.7%)	**-20%** (-36.2 to -3.9)
Other physical handicap, such as blindness, deafness, muscle disorder or metabolic disease	108 (76.1%)	29 (70.7%)	5.3% (-10.3 to 20.9%)
Expected death before, during or within a month after birth	128 (90.1%)	34 (82.9%)	7.2% (-5.3 to 19.7%)
Limited life expectancy (until 30 years old; for example, cystic fibrosis)	79 (55.6%)	22 (53.7%)	2.0% (-15.4 to 19.3%)
Disease occurring later in life	46 (32.4%)	4 (9.8%)	**22.6%** (10.7 to 34.5%)

Bold = statistically significant. TOP = Termination Of Pregnancy

Table 2 presents the Dutch and Israeli professionals' opinions about the estimated burden of an oral cleft and its impact on happiness and overall life functioning for afflicted children and their parents. Using a similar scale from 0 to 100, the Dutch professionals' responses indicated that they viewed the repair of oral cleft as a more serious burden for children and parents than the Israeli professionals did: the reported scores were 59.5 and 34.7 [mean difference 24.8, 95% CI 15.7 to 33.9] for children and 63.0 and 40.9 [mean difference 22.1, 95% CI 13.4 to 30.8] for parents, respectively. Conversely, compared with the Israeli professionals, the Dutch professionals thought that an oral facial cleft had less effect on a child's overall functioning [21.4 and 11.3, respectively; mean difference -10.1 95% CI -17.2 to -2.9]. There was no difference between the Dutch and Israeli professionals' opinions regarding the influence of an oral cleft on the happiness of the children or their parents.

Table 2 *Professional opinions about oral cleft*

Question	The Netherlands (N = 142) Mean (sd)	Israel (N = 41) Mean (sd)	Mean differences (95% CI)
How seriously do you think the oral cleft treatment will burden the child?	59.5 (23.8)	34.7 (28.9)	**24.8** (15.7 to 33.9)
How seriously do you think the oral cleft treatment will burden the parents?	63.0 (22.4)	40.9 (27.6)	**22.1** (13.4 to 30.8)
How seriously do you think this will affect the child's happiness?	27.7 (21.5)	24.7 (22.9)	2.9 (-5.2 to 11.0)
How seriously do you think this will affect the parents' happiness?	27.8 (21.5)	31.2 (30.4)	-3.4 (-12.0 to 5.2)
How seriously do you think this will affect the child's overall functioning?	11.3 (14.6)	21.4 (31.1)	-**10.1** (-17.2 to -2.9)

Bold = statistically significant. All answers were given on a scale from 0 (not serious) to 100 (very serious)

DISCUSSION

The results of this study show that a minority of obstetric care providers in the Netherlands and Israel favor TOP in case of isolated oral cleft. This percentage was comparable in both countries (11%). This is in contrast to the high number of

parents in Israel who choose TOP in case of an isolated oral cleft[9]. Because obstetric care providers in the Netherlands and Israel reported comparable positive opinions about oral clefts, we conclude that their personal beliefs therefore cannot explain the dramatic difference in TOP rates between these two countries.

Several studies have attempted to explain the differences in parental decisions about TOP among countries[13,16,17]. A combination of factors play a role, including the child and family's best interest, the severity of the abnormality, economic issues, the treatment burden, religious background, legal restrictions and gestational age at the time of diagnosis. The latter three factors were the only well-defined issues in both the Netherlands and Israel. Routine prenatal ultrasound is offered in both the Netherlands and in Israel, and participation is higher than 95% in both countries[2,17]; however, the gestational age at which ultrasound is offered differs. In Israel, women are offered an ultrasound between 14 and 16[9] weeks gestation, whereas in the Netherlands, ultrasound is performed at 20 weeks. It may be easier to make the difficult decision to terminate a pregnancy at an earlier gestational age. In both countries, late TOP is legal. Additionally, religion differs in Israel and the Netherlands. In Israel, according to Jewish law, the interruption of pregnancy is generally forbidden after 40 days of pregnancy, and Islamic Law absolutely forbids TOP after the 120th day of pregnancy. However, the majority of the Jewish population is secular and considers TOP to be legitimate[18]. In the Netherlands, the majority of people are not religious (62% according to the Netherlands Institute for Social Research; only 17% believe that their religion is very important). Both countries have very religious minorities. In conclusion, religious doctrine does not seem to explain the large difference in TOP rates. Moreover, no specific research has evaluated how religious beliefs influence decisions about TOP when an isolated oral cleft is suspected.

In addition to technical, legal and religious issues, parental attitudes towards oral clefts no doubt play an important role in the decision to terminate a pregnancy. Parents' personal views affect their perception of the severity of the condition, and they are also influenced by the medical ramifications, which depend on and are mediated by the care provider's counseling[10,24,25]. Thus, the care providers' perception of the severity of an oral cleft matters. In this survey, we showed that the majority of care providers

considered oral clefts a disability or a cosmetic defect and that there were no major differences in this rating between the countries. Whether an individual judges an oral cleft as severe or not severe is both culturally and socially determined[3]. In a study by Wyszinski et al.,[16] 37.9% of the parents of children with an oral cleft in Argentina considered it a 'trait'. In contrast, parents interviewed in Saudi Arabia worried that "ladies with oral clefts will have a hard time finding a husband and will not have a normal social life, so termination of such an abnormality will be better"[26]. In our study, we showed that Israeli and Dutch care providers judged the severity of an oral cleft similarly, so this could not explain the differences in TOP rates. In addition, Some of the respondents in this study stated that their opinion was insignificant for deciding whether isolated oral cleft was a reason for TOP. They stated that the decision to terminate the pregnancy was ultimately the parents'. Although we agree that decisions regarding TOP in case of an affected fetus are and should be the parents', counselors should be able to empower the parents to be able to make an autonomous choice. It is the counselor's responsibility to inform parents about the etiology, pathogenesis and associated anomalies as well as the medical, surgical, and clinical needs of a child with an oral cleft. However, a former study[19] showed that many parents were unsatisfied with the initial information they received at the ultrasound unit. In the study by Hsieh[20] and Rey-Bellet[21], some mothers expressed feeling anxious about their baby's condition, and, because of the limited information provided by professionals, some even feared that the condition might be associated with impaired intelligence. Therefore, the input from a cleft lip and palate team during the prenatal period is of utmost importance.

Usually, the diagnosis of an oral cleft comes as a shock to parents, and proper counseling helps to reduce the anguish of having a baby with an oral cleft[22]. To reduce anxiety and uncertainty, clear and consistent information about the anomaly and its treatment, etiology and prognosis must be provided during initial counseling[12,23]. Kuttenberger et al. suggest[23] that such counseling should be provided by a multidisciplinary cleft lip and palate team, a position that we support. Moreover, our study shows that it is uncommon for an obstetrician to detect an oral cleft, whereas cleft lip and palate teams have the expertise required to treat children with oral clefts in daily practice.

Unfortunately, this study provides no information about possible differences in the counseling techniques used by obstetric care providers in Israel and the Netherlands.

It remains unknown whether all parents in Israel who choose TOP in the case of an isolated oral cleft were willing or able to consult a cleft lip and palate team before making their decision. This service is routinely offered in the Netherlands. This area warrants further research because possible differences in actual counseling practices between Israel and the Netherlands may explain part of the variation in TOP rates despite the fact that gynecologists in both countries hold similar personal opinions about cleft and TOP.

The major strength of this study is its comparison of two countries in which TOP rates for isolated cleft differ markedly . Moreover, this is the first study to survey professional opinions about oral clefts. Our study has some methodological shortcomings. First, although a response rate of approximately 40% might seem low, it is common for anonymous medical surveys[27]. This rate could even be considered high because the questionnaires were distributed by e-mail rather than administered in person. Second, there was a baseline difference in the responses depending of the respondent's profession. Subgroup analyses that included only gynecologists showed similar results (data not shown). Finally, the actual response rate in Israel could only be estimated because the exact number of Israeli gynecologists that perform prenatal ultrasounds is not known, although an independent nationwide survey reported that there were 100 such gynecologists[17].

CONCLUSION

Prenatal care providers in the Netherlands and Israel do not differ in their opinions on the severity of oral clefts and the acceptability of TOP for an isolated oral cleft. This study shows that provider opinion does not explain the dramatic difference between these countries in TOP for isolated oral cleft. It can be expected that in the future, ultrasound sensitivity for detecting oral clefts will only increase, resulting in a greater number of prenatally diagnosed clefts. Although counseling factors were not studied, we advise gynecologists to refer parents to a cleft lip and palate team prenatally. It is important to provide parents who are expecting a child with an oral cleft with balanced counseling and adequate information.

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Parental attitude on prenatal diagnosis of cleft lip and palate; a prospective cohort study

Submitted

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ABSTRACT

Objectives The prenatal diagnosis of oral clefts (OCs) by ultrasound can pose an ethical dilemma. The purpose of this study was to obtain additional insight into the psychosocial and moral considerations of prospective parents concerning OCs, the burden of OCs and parents' attitude toward possible termination of pregnancy (TOP) to improve counseling in the future.

Study design Between August 2011 and August 2014, a prospective cohort questionnaire study was administered to parents visiting our prenatal clinic.

Results Most of the parents described an oral cleft as a cosmetic disability (43.6%) or as "just a little different" (26.6%). These parents expected that the OC would not affect their own happiness or the happiness of their future child. Health professionals had a considerable influence on parental opinion. A minority (6.4%, 5/85) of the respondents considered TOP, and none of the participants chose to terminate the pregnancy. The estimated severity of the oral cleft and the estimated influence on the child's happiness both had a significant influence on whether TOP was considered (p=0.04).

Conclusions This study suggests that the active involvement of cleft lip and palate teams is worthwhile. Caregivers should be aware that their counseling is important in the decision making of parents.

INTRODUCTION

The finding of a facial malformation on prenatal ultrasound can be a major psychosocial burden for parents, who might express signs of severe distress [1-3]. The most common congenital facial malformation is oral cleft (OC), which arises in approximately 1 of 700 live births [4]. As the use of routine scanning of the face with ultrasound has become standard, prenatal diagnosis of OCs is now possible and accounts for a detection rate of 88% [5]. In response, specialized prenatal cleft clinics participate in the counseling of parents expecting a child with a possible OC [6] to help them cope with the news and prepare them for the birth of their child.

There is controversy concerning the preferred consequences of the prenatal detection of malformations. In addition to the parental issues, there are social and ethical implications of a prenatal diagnosis [7]. The advantages of prenatal knowledge are that parents can psychologically prepare for the anomaly, there is an opportunity for education, parents can plan neonatal care, and there is an opportunity to perform genetic counseling [3, 5, 8]. However, parents may experience emotional disturbance of the pregnancy once they know their child has an OC [1]. Further disadvantages of the prenatal detection of a cleft include the imprecision of the diagnosis [9], impossibility of fetal surgery in nearly all cases, and general concern regarding the increased number of terminations of pregnancy (TOPs) of fetuses with an isolated OC [10, 11]. Nonetheless, it is widely accepted that most parents prefer to know the diagnosis prenatally than be confronted with the anomaly after birth [1, 2, 8, 9, 12, 13].

For optimal counseling, it is imperative to comprehend the experience of receiving a diagnosis of an OC during the prenatal period. However, all previous studies assessing the impact of a prenatally detected OC are of retrospective design, implying that, at the time of assessment, the child was already born. The latter scenario might affect a parent's view on the impact of an OC diagnosis. Consequently, the parents' perspective regarding the expected severity, burden and possible TOP of a fetus with OC in the prenatal period is unknown. The purpose of this study was to obtain additional insight into the psychosocial and moral considerations of prospective parents concerning

OCs, the burden of OCs and parents' attitudes toward possible TOP as well as their opinions regarding current counseling to improve future counseling.

MATERIALS AND METHODS

Prenatal consultation

In The Netherlands, a routine screening two-dimensional (2D) ultrasound is offered to all pregnant women at approximately 20 weeks of gestation [6]. If an anomaly is suspected, the mother is referred to a tertiary care center, where a more elaborate 2D/3D ultrasound is performed to confirm the diagnosis. Moreover, parents are given advice concerning possible genetic counseling. If an OC is diagnosed, parents in the region of Utrecht are invited to visit a special outpatient clinic where counseling is performed by a plastic surgeon and a medical physiologist from the cleft lip and palate team. The purpose of the counseling is to offer parents information concerning etiology, pathology, treatment, and prognosis as well as psychosocial aspects and advice regarding postnatal feeding. Specifically, parents receive written information about treatment and pre- and post-surgical photographs of children with an OC.

Study design

A prospective cohort study was performed between August 2011 and August 2014. All of the parents visiting the prenatal cleft clinic for their unborn child with an isolated OC were asked to participate in the study by answering a questionnaire. The medical psychologist acquired informed consent. Only Dutch-speaking parents were included due to linguistic issues. The parents were asked to participate after they received counseling by the cleft lip and palate team.

Questionnaires

The questionnaire used in this study was derived from one previously published by Korenromp et al.[14], who examined parental opinion on prenatally detected Down syndrome. The questionnaire consisted of four parts (full version available online). The first part provided basic information, such as sociodemographic and medical

characteristics, including a family history of OC, religion, and expected characteristics of the child's OC. In the second part of the questionnaire, parents were asked to describe OCs in general and about their thoughts and attitudes toward the impact and expected burden of the OC of their child. Furthermore, the parents were asked to describe the people who influenced their opinion of OC. In the third part, the parents were asked whether TOP would ever be an option and, what factors influenced their decision. Finally, parents rated the prenatal counseling. Parents individually filled out an extensive standardized questionnaire. Hence, two questionnaires per child were obtained. Questionnaires were analyzed anonymously.

Statistical analysis

Questionnaire data were summarized using descriptive statistics—i.e., frequencies or medians with interquartile ranges (IQRs) per question. Two groups were compared: those who did and those who did not consider TOP as an option in the case of an OC. Furthermore, obstetric characteristics were compared between those mothers who did and those who did not return the questionnaire to assess whether these baseline characteristics were comparable. The descriptions of an OC were compared among the different types of OCs. All of the comparisons were made using chi-squared statistics for dichotomous or the non-parametric Mann-Whitney U-test for continuous outcomes. A p-value < 0.05 was considered statistically significant. Analysis was performed using SPSS version 20.0 [15].

Ethics

The medical ethical commission of the University Medical Center Utrecht approved the study (nr 09/207), for which all participants provided informed consent.

RESULTS

Participants

During the study period, 81 couples expecting a child with an isolated OC were referred to the tertiary clinic (see figure 1). One couple decided to terminate the

pregnancy after the diagnosis of OC was confirmed in the tertiary clinic. This couple was offered consultation by the cleft team, but contact was never made. Twenty-one couples were excluded. Seven couples declined to participate, resulting in 52 couples (52 women and 50 partners) being included in the study after signing the informed consent. Seven couples did not return the questionnaire, and only the mother's questionnaire was received for three couples, leading to a response rate of 83.3% (85/102). The baseline characteristics of the participating couples are shown in table 1. There were no significant differences between responders and non-responders in terms of the weeks of gestation with detection and inclusion, type of OC or obstetric history (data not shown).

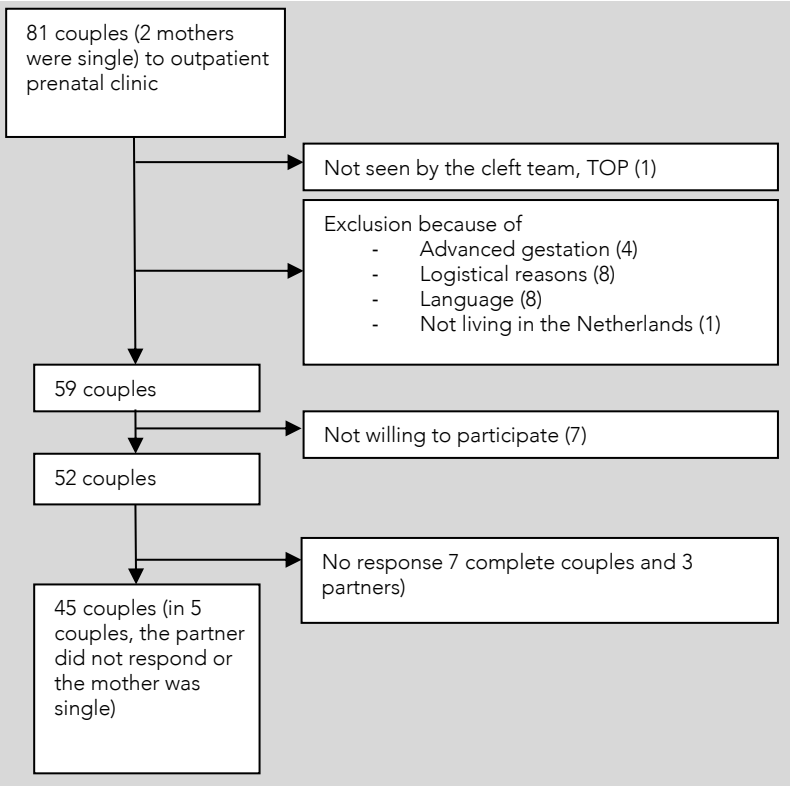

Figure 1 *Flowchart inclusion*

Table 1 *Baseline characteristics of pregnant women and their partners expecting a child with an OC*

Characteristics	Responders (n=85)
Gestation, weeks at detection, median (IQR)	20 (19.3-20.0)
OC confirmed in tertiary care center after first detection on US, in days, median (IQR)	2 (1.0-7.0)
Gestation, weeks at study inclusion, median (IQR)	23 (22.0-26.0)
Expected type of cleft	
Cleft lip (alveolus)	39 (45.9)
Cleft lip and palate, unilateral	27 (31.8)
Cleft lip (and palate), bilateral	17 (20.0)
Cleft palate	2 (2.4)
Children with physical abnormality in the family	4 (4.8)
Already have children with OC	2(2.4)
Former spontaneous abortions	24 (28.2)
Former terminations of pregnancy	3 (3,5)
Age, years, median (IQR)	31 (28-36)
Marital status	
Married	54 (65, 1)
Cohabiting	27 (32.5)
Single	2 (2.4)
Education	
Lower high school education	16 (19.8)
Secondary school education	27 (33.3)
College or academic education	38 (46.9)
Occupation	
Working full time (> 80%)	53 (65.4)
Working part time (< 80%)	18 (22.2)
Homemaker	4 (4.9)
Unemployed	5 (6.2)
Student	1 (1.2)
Religious	42 (50.6)
Religion influences important decisions	27 (31.8)
Have an OC themselves	9 (10.8)
Family history of OC	6 (7.2)

Figures are absolute numbers (percentages) unless stated otherwise.
IQR = Interquartile range.

Thoughts concerning OCs and expected burden of OCs

Table 2 describes parents' thoughts concerning OCs and the expected burden of OCs. Most of the parents described an OC as a cosmetic disability (43.6%), followed by those considering an OC as "just a little different" (26.6%). A minority thought of an OC as a handicap (10.6%), a disorder (2.1%) or a disease (1.1%). The description of cleft was not significantly different among the different cleft types (p=0.29). Parents who described an OC as a trait, a cosmetic disability or "just a little different" rated the influence of the OC on their child's happiness as 10.0 on the scale of 0-100 (IQR, 0.00-23.75). Parents who described an OC as a condition, a handicap, a disorder or a disease rated this influence as 27.5 (IQR, 12.5-55.00) (p=0.01). For these two groups, regarding the influence of their child's OC on parents' personal happiness, the median scores were 5.00 (IQR, 0.00-15.00) and 20.00 (IQR, 10.00-50.00), respectively (p=0.00). The parents' opinion of OCs was mostly influenced by their partner (significant influence in 76.5%; 62/85) and least influenced by society (significant influence in 7.9%; 6/85). Among the group of health professionals, the obstetrician (41%, 32/85), plastic surgeon (54.3%, 44/85) and psychologist (20.8%, 16/85) were found to have a significant influence on the parents' opinions regarding OC.

Table 2 *Thoughts about OC and the expected burden of OC*

Questions	Total (n = 85)
How would you describe an OC (more than one answer possible)? †	
Trait	7 (7.4)
Cosmetic disability	41 (43.6)
Just a little different	25 (26.6)
Condition/Physical defect	8 (8.5)
Handicap/Disability	10 (10.6)
Disorder	2 (2.1)
Disease	1 (1.1)
How serious, on a scale from 0 (not serious) to 100 (very serious), do you think the OC found on US is? Median (IQR)	50 (30-70)
How will the OC, on a scale from 0 (not much) to 100 (very much), affect the happiness of your future child? Median (IQR)	20 (0-30)
How will the OC, on a scale from 0 (not much) to 100 (very much), affect your personal happiness? Median (IQR)	7.5 (0-23.75)

Figures are absolute numbers (percentages) unless stated otherwise.
IQR = Interquartile range.
† =Multiple answers possible.

Attitudes toward the termination of pregnancy

A minority of participants (6.4%, 5/85) considered TOP, and none chose to terminate the pregnancy. The parental attitudes toward TOP in general and toward TOP in the case of an OC are described in table 3. Most parents did not feel that they had to defend their decision to continue the pregnancy (95.1%, 77/85), and they did not perceive pressure regarding this decision. In contrast, the majority of the participants thought that TOP could be an option in some situations (75.3%, 58/85). For example, 41.1% of the participants reported that TOP would be an option in the case of Down syndrome. The estimated severity of the OC ($p=0.03$) and its estimated influence on the happiness of the child ($p=0.04$) were related to the consideration of TOP. Type of OC, religion, family history of OC and estimated influence on the parents' personal happiness were not of significant influence.

Rating of the counseling by the cleft team

More than half of the participants reported that they needed professional support after the discovery of an OC during pregnancy (57.7%, 45/85) (table 4). Overall, participants were (very) satisfied with the information.

Table 3 *Attitudes toward termination of pregnancy (TOP)*

Questions	Total (n =85)
Considered terminating this pregnancy	5 (6.4)
Do you feel like defending continuation of pregnancy to other people?	
Somewhat	1 (1.2)
Hardly	3 (3.7)
Not at all	77 (95.1)
Is anyone putting pressure on you regarding the decision to continue or terminate the pregnancy?	
Partner	3 (3.7)
Family/Friends	1 (1.3)
Medical professionals	2 (2.5)
Religious community	1 (1.3)
Norms from society	1 (1.3)
TOP can, in my opinion,	
- never be an option	19 (24.7)
- be an option in some situations	58 (75.3)
Are there any circumstances in which TOP would be an option for you? †	
Down syndrome (trisomy 21)	24 (41.4)
Intellectual disability or disorder	23 (39.7)
Wheel chair dependency	14 (24.6)
Other physical defect (such as blindness/deafness/ muscle or metabolic disease)	9 (15.5)
Life expectancy less than one month after birth	48 (82.8)
Life expectancy < 6 months	46 (79.3)
Life expectancy < 30 years	7 (12.1)
Expected to have a disease later in life	2 (3.4)

Figures are absolute numbers (percentages) unless stated otherwise.
† = Multiple answers possible (total can exceed 100%).

Table 4 *Opinions about counseling*

Questions and ratings	Total (n=85)
Need for professional support	45 (57.7)
Need for contact with peers	23 (27.7)
Satisfaction about findings and consequences	
(Very) satisfied	78 (65.1)
Neutral	4 (4.9)
(Very) unsatisfied	-
Satisfaction with postnatal preparation	
(Very) satisfied	65 (83.3)
Neutral	11 (14.1)
(Very) unsatisfied	2 (2.6)
Satisfaction with professionals	
Obstetrician	
(Very) satisfied	64 (79)
Neutral	8 (9.9)
(Very) unsatisfied	1 (1.2)
N/A	8 (9.9)
Plastic surgeon	
(Very) satisfied	63 (75.9)
Neutral	5 (6)
(Very) unsatisfied	2 (2.4)
N/A	13 (15.7)
Psychologist	
(Very) satisfied	39 (50)
Neutral	7 (9)
(Very) unsatisfied	1 (1.3)
N/A	31 (39.7)
Social Worker*	
(Very) satisfied	19 (23.4)
Neutral	3 (3.7)
(Very) unsatisfied	-
N/A	59 (72.8)

Figures are absolute numbers (percentages).
*** Some parents may have confused the social worker with the psychologist.**
N/A = not applicable

COMMENTS

Since the introduction of prenatal scans as the standard of care in the Netherlands, OCs are often diagnosed before birth [16]. The prenatal diagnosis of OCs has been argued to increase the likelihood of TOP [9, 10]. However, the findings of this study demonstrate

that most future parents in the Netherlands believe that an isolated OC is a cosmetic disability or "just a little different" and, therefore, is not a reason for TOP. Health care professionals had significant influence on the parents' perceived thoughts regarding OCs, particularly the obstetrician and plastic surgeon of the cleft lip and palate team.

Perceived burden of OCs

In this study, parents seemed not to perceive OCs as a serious medical condition, and they believed the cleft would not be of influence on the happiness of their future child. Other studies showed dissimilar perspectives regarding the burden of OCs and fear of stigmatization. Parents perceived the defect as severe [17, 18], feared for the intelligence of the child [2] and were anxious about the child's self-esteem and self-image [19]. The relatively positive attitude concerning OCs in this study may be explained by several factors. First, the questionnaire was administered after counseling, suggesting the importance of the counseling by our cleft lip and palate team. Second, the positive attitude may be a consequence of the timing of the study inclusion; parents were pregnant and had not yet seen their child with OC born. Third, these results must be placed within the context of the Dutch Health Care System, where excellent services for people with disabilities are offered and the entire treatment (0-18 years) is always covered by medical insurance [20]. Fourth, one could argue that Dutch society is tolerant of people with disabilities. Although this study did not address the emotional distress of the prenatal diagnosis of OCs, previous studies showed guilt, anxiety and sadness as common sentiments after the prenatal diagnosis of an OC [1, 2, 13]. A person with an OC is often characterized as one who shows difficulty in speaking or someone with a scarred face [2]. Moreover, on the internet, "worst-case scenario pictures" are often circulated [1]. Therefore, it is extremely important that the cleft lip and palate team be actively involved in prenatal counseling [3], can explain treatment options and the expected difficulties with speech and hearing problems and can show realistic pictures of postoperative results. Finally, this study showed that more than half of the participants reported that they needed professional support after the discovery of an OC during pregnancy. The psychologist on the cleft lip and palate team can conduct a psychological assessment and provide appropriate referrals if needed [1, 21].

Attitudes toward TOP

In the literature, there are striking differences among countries with respect to TOP rates for OC. During our study period, only one couple decided to terminate the pregnancy, whereas 95.6% of the parents never considered TOP. These figures are in accord with results from Argentina [22] and the UK [13], where none and 7.5% of the parents considered TOP, respectively. Our results are in sharp contrast with those from Israel [10] and Taiwan [19], where 93.4% and 53.1% of the affected fetuses, respectively, were aborted. A variety of factors are suggested to be responsible for these differences, such as religious, legal, social, cultural and financial circumstances [8]. The present study found that the perception of burden—or the estimated severity of the cleft—and estimated influence of OC on the happiness of the future child were significant factors for the decision to consider TOP. Although this study could not compare results with countries where TOP for OC is common, it is possible that the burden of OCs in these countries is perceived as more serious. Although religion and legal issues were not a significant factor in the consideration of TOP, it can be argued that, in countries such as Argentina, where TOP is legally restricted and most of the people are active participants in the Catholic faith, these factors do play a role [22]. In the Netherlands, TOP has been legalized since 1981. For example, more than 95% of couples in the Netherlands opt for TOP in the case of prenatally diagnosed Down syndrome [23]. In our study, 75.3% of the parents stated that TOP could be an option in some situations. This finding also indicates that OCs are not perceived as serious, and thus, most parents did not consider TOP.

Evaluation of prenatal counseling

In general, in this study, parents were satisfied with the prenatal counseling. It should be understood that, in our facility, prenatal counseling is a team effort (obstetrician, plastic surgeon and medical psychologist) and is conducted regularly. The obstetrician repeats an anomaly scan in the presence of the partner, plastic surgeon and medical psychologist. Subsequently, there is ample time reserved for counseling (45 min) by the plastic surgeon and medical psychologist. Thus, our psychologist and plastic surgeon are actively involved in facilitating the process of coping with the diagnosis and in the discussion of future perspectives, respectively. More specifically, the ultrasonic three-dimensional view allows the plastic surgeon to tailor prenatal counseling to

the exact OC type, including its severity and anticipated postnatal management. The involvement of plastic surgeons during the prenatal phase is a relatively new phenomenon. Kemp et al. showed that the anxiety of prospective parents was significantly reduced by the counseling of a pediatric surgeon [21]. Cleft lip and palate teams have extensive experience treating children with OC. During the study period, there was one couple that decided, before talking to the cleft lip and palate team, to terminate the pregnancy. Although we find counseling of utmost importance to future parents, they cannot be forced to participate [9].

Methodological issues

This is the first study to prospectively investigate consecutive parents and, in contrast to previous research, included a relatively large number of participants. Hence, this study involved a homogeneous population only featuring isolated clefts, thereby correcting for case-mixing with more severe cleft forms. The response rate of 83.3% was fairly high considering that the risk of sample bias was low. Moreover, there were no significant differences between responders and non-responders. Finally, participants were included during pregnancy, and thus the option to terminate the pregnancy was realistic at 20 weeks of gestation. Because previous studies concerning coping with the prenatal diagnosis of clefts were of retrospective and cross-sectional design [1, 2, 8, 9, 12, 13, 24, 25], their results not only might contain ascertainment bias but also might have influenced parental attitudes toward OC because the children were already born and/or treated (surgically). Furthermore, in contrast to other studies, the process of counseling in our study was uniform because there was always a plastic surgeon and psychologist from the cleft lip and palate team involved [1, 12].

Some limitations of this study can be noted. For example, because there were no parents in the study population who actually chose TOP, we could only compare groups of parents who did and did not consider TOP. Additionally, the results revealed by this study may not be applicable to other populations than the Dutch due to cultural, religious and socioeconomic factors known to influence parental reproductive choices [22]. Finally, questionnaires were assessed after parents had been counseled; thus, no conclusions can be drawn about the influence of counseling on the opinions and attitudes of parents.

In conclusion this study is the first to describe the thoughts and attitudes of parents expecting a child with an isolated OC during pregnancy. Dutch parents did not perceive an isolated OC as a severe condition, and most did not consider terminating the pregnancy. Future parents reported that they needed professional support and that they were satisfied with the existing multidisciplinary prenatal counseling. These results confirmed that active involvement of cleft lip and palate teams is extremely helpful. Greater awareness of parental experiences demonstrated that a realistic picture of OC should be presented to the parents without fear that the parents would interpret the given information as undesirable. Additionally, professionals should be aware of their authority while counseling because, regardless of the positive or negative effect, they have significant influence on parents' opinions concerning OC.

ACKNOWLEDGEMENTS

The authors would like to thank the parents of the children born with an oral cleft during the years 2011-2014 for participation in this study. The authors would further like to thank G.T.R. Manten, obstetrician of the Wilhelmina Children's Hospital in Utrecht, the Netherlands for her helpful discussion and critically reading of the manuscript.

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QUESTIONNAIRE

GENERAL QUESTIONS

For the medical psychologist
1. What type of clefting can be seen on the ultrasound?
O unilateral cleft lip
O unilateral cleft lip and jaw
O unilateral cleft lip, jaw and palate
O cleft palate without cleft lip
O bilateral cleft lip
O bilateral cleft lip and jaw
O bilateral cleft lip, jaw and palate

For the mother/father
2. Age
..... years old

3. Civil status
O married
O co-habiting
O long-distance relationship
O widow/widower
O divorced
O single

4. If necessary: how long have you been living with your current partner?
..... year

5. Education
O Elementary school
O High school
O University or similar

6. Job status
O (almost) full time (80 % or more)
O part-time (less than 80 %)
O housewife/man
O unemployed/on welfare
O student
O other:...

7. If religious, what faith do you adhere to?
O Religious but no specific faith
O Islam
O Judaism
O Christian
O not religious
O other:...

QUESTIONS ABOUT ANY PREVIOUS PREGNANCIES

8. Is this your or your wife's first pregnancy?
O yes
O no, the .....

9. Have you or your wife ever had a spontaneous miscarriage?
O yes, ... times
O no

10. Have any pregnancies ever been aborted?
O yes, ... times
O no

11. If yes, what was the reason?
O spontaneous abortion ..... times
O unwanted pregnancy ..... times
O congenital defect(s) in your child ..... times
O health risk in yourself ..... times

12. Do you have children?
O yes, ... child(ren) O no

If yes, do any of these children have any kind of congenital deformities?
O yes, ... child(ren) O no
If yes, which?.....

QUESTIONS CONCERNING THE PRENATAL RESEARCH

13. How did the pregnancy come about? (one answer only)
O as planned
O planned, but having to wait for over a year
O through fertility treatment
O not planned, yet welcome
O not planned, having no specific child-wish

14. How far on in the pregnancy are you now?
..... weeks

15. How far on was the pregnancy when the first heart beat was heard?
O ..... weeks O never heard any heart beat

16. Have you already felt the child move (not for the man)?
O yes O no

17. How far on was the pregnancy when cleft was first suspected?
..... weeks

18. How long after did you have to wait for the final results?
..... days

19. Before the ultrasound, did you ever think your child might suffer from a congenital defect?
O yes O no

If you ever thought your child might have cleft, why did you think this? (several answers are possible)
O I already have a child with cleft
O there is a history of cleft in my/our family
O I always consider all possibilities
O other: .....
O I never considered this

20. What led to repeating the prenatal check (several answers are possible)
O something didn't seem right during the check-up
O something didn't seem right during the routine ultrasound
O age indication
O I already have a child with cleft
O My family has a history of disorders/ deformities
O My partner's family has a history of disorders/ deformities
O use of medication
O I wanted to be completely sure about the health of my child
O other: .....

21. How was the cleft discovered? (several answers are possible)
O routine ultrasound
O ultrasound aimed at another specific illness
O other:. .....

22. Had you already decided to terminate the pregnancy in case of certain illnesses before you and your partner decided on a prenatal check?
O yes O no
O no, I was still hesitating O I don't remember

23. Did you doubt the correctness, reliability of the results?
O yes and I still do
O yes, I couldn't believe it at first
O no

Now you will be asked to make some assessments.

Example: you want to answer the question "How certain were you....." with:
"pretty certain, but I was still hesitating", then you could put a little cross like this
|---------|---------|---------|---------|---------|---------X---------|---------|---------|---------|
Absolutely uncertain Absolutely certain

24. How certain are you that your child will suffer from cleft (after the ultrasound)?
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
Absolutely uncertain Absolutely certain

25. How serious do you think the diagnosed cleft will be?
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
Not serious Very serious

26. What do you think the chances are of more or other defects in your child?
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
0% 100%

27. How seriously do you think this will affect the happiness of your child?
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
Not seriously Very seriously

28. How seriously do you think this will affect your own happiness?
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
Not seriously Very seriously

29. How would you define cleft?
O a feature/characteristic (like 'bleu eyes' or 'dark hair')
O a little different from normal
O a condition
O a handicap/defect
O a disorder
O an illness

32. Have you considered terminating the pregnancy?
O yes and I will decide to do so
O yes, I have considered it, but will not do so
O no
O it hasn't crossed my mind

33. Are there certain circumstances (as mentioned here below) where a termination could very well be an option (several answers are possible)
O Down syndrome
O other mental handicap or disorder
O wheelchair dependency
O other physical handicap or affection such as, deformities, blindness, deafness, muscle disorders or metabolic disease
O expected death before, during or within a month after birth
O very short life expectancy (until six months)
O limited life expectancy (until 30 years old)
O disease occurring later in life
O other: .....
.....

QUESTIONS ABOUT THE DECISION MAKING PROCESS

34. Has the possibility to terminate the pregnancy been discussed with you by professional counsellors?
O yes
O no

35. Do you feel you (and/or your partner) have been pressurized?
O very much so
O rather
O somewhat
O not really
O not at all

36. To what degree have the following people influenced your experiencing the cleft of your child? Please tick the appropriate answer.	1. substantially 2. considerately 3. somewhat 4. hardly 5. not at all 6. does not apply					
Gynaecologist	1	2	3	4	5	6
Obstetrician	1	2	3	4	5	6
Clinical geneticist	1	2	3	4	5	6
Social worker	1	2	3	4	5	6
Medical psychologist	1	2	3	4	5	6
Plastic surgeon	1	2	3	4	5	6
General Practitioner	1	2	3	4	5	6
Spiritual counsellor	1	2	3	4	5	6
Partner	1	2	3	4	5	6
Parents (in law)	1	2	3	4	5	6
Other family members	1	2	3	4	5	6
Friends	1	2	3	4	5	6
People in a similar situation	1	2	3	4	5	6
Society	1	2	3	4	5	6
Other:						

37. To what degree have the following people influenced your decision to carry out the pregnancy (fill out only when you had doubts about doing so)? Please tick the appropriate answer.	1. substantially 2. considerately 3. somewhat 4. hardly 5. not at all 6. does not apply					
Gynaecologist	1	2	3	4	5	6
Obstetrician	1	2	3	4	5	6
Clinical geneticist	1	2	3	4	5	6
Social worker	1	2	3	4	5	6
Medical psychologist	1	2	3	4	5	6
Plastic surgeon	1	2	3	4	5	6
General Practitioner	1	2	3	4	5	6
Spiritual counsellor	1	2	3	4	5	6
Partner	1	2	3	4	5	6
Parents (in law)	1	2	3	4	5	6
Other family members	1	2	3	4	5	6
Friends	1	2	3	4	5	6
People in a similar situation	1	2	3	4	5	6
Society	1	2	3	4	5	6
Other:						

38. Perhaps you have had the feeling not being able to choose. If that is the case, what brought on that feeling?
.....
.....
.....
.....
.....
.....
O does not apply, since I feel I have had a choice

39. If you feel pressurized when making a decision, who is pressurizing you? (several answers are possible)
O partner
O family/friends
O medical team
O congregation
O the values within society
O other: .....
O does not apply as I don't feel pressurized

40. Do you and your partner agree on the decision to carry out the pregnancy?
O does not apply/no partner
O no
O yes

41. If there are people around you with cleft or any other congenital defect, does that influence your decision to carry out the pregnancy?
O very much so
O rather
O somewhat
O not really
O not at all
O does not apply; I don't know anyone with cleft or any other congenital defect

42. Are you having doubts about carrying out the pregnancy?
O very much
O rather
O somewhat
O not really
O not at all

43. If you are having doubts, what causes them? (several answers are possible)
O being overwhelmed
O It is against my faith/ outlook on life
O I didn't know much about the diagnosed defect
O I had the feeling I was killing a child
O I doubted the diagnosis
O the diagnosis was uncertain
O my partner and I did not agree
O I couldn't oversee the consequences
O my mind and my heart were struggling
O fear about the procedure (pain, complications)
O other: .....
.....
.....
.....
.....

44. Have you had to defend your decision to carry out the pregnancy towards certain people?
O very much
O rather
O a little
O hardly
O no

QUESTIONS ABOUT SUPPORT

45. Are you in need of support?
O yes, alone
O yes, with partner
O yes, in a group
O no
O other: ……

46. Does your belief influence the major decisions in your life? (one answer only)
O always
O often
O sometimes
O rarely
O never
O does not apply

47. Do you feel supported by your belief in this experience? (one answer only)
O very much
O rather
O somewhat
O no
O on the contrary
O does not apply

48. Have your convictions changed after what has happened?
O yes, they have become stronger
O they have remained the same
O no, I've had more doubts
O does not apply

49. In case of problems or difficulties, how many people around you – with the exception of your partner – can you rely on for true support?
..... people

QUESTIONS ABOUT THE COUNSELLING

51. What did you think about the course of actions in the ultrasound practice and at the Wilhemina's Childeren Hospital around or during the prenatal check? Do you have any suggestions or criticism?
.....
.....
.....
.....
.....
.....
.....
.....

52. How satisfied are you with the given information?	1. very satisfied 2. rather satisfied 3. neutral 4. rather dissatisfied 5. very dissatisfied				
About the prenatal check	1	2	3	4	5
About the results and the consequences of the check	1	2	3	4	5
About carrying out the pregnancy and preparing the birth of a child with cleft	1	2	3	4	5

53. Are you satisfied with the counselling received?	1. very satisfied 2. rather satisfied 3. satisfied as well as dissatisfied 4. rather dissatisfied 5. very much dissatisfied 6. never had any contact					
Gynaecologist	1	2	3	4	5	6
Obstetrician	1	2	3	4	5	6
Clinical geneticist	1	2	3	4	5	6
Social worker	1	2	3	4	5	6
Medical psychologist	1	2	3	4	5	6
General Practitioner	1	2	3	4	5	6
Plastic Surgeon	1	2	3	4	5	6
Spiritual counsellor	1	2	3	4	5	6
Other:						6

54. What did you not like about the counsel?

.....

.....

.....

55. What did you like about the counsel?
.....
.....
.....

56. What could be improved about the counsel?
.....
.....
.....

57. At this moment, do you feel the need to contact other parents whose child has been diagnosed with cleft on the ultrasound and/or parents who already have an older child with cleft?

O yes, very much so
O yes, actually
O no, not really
O no, not at all

STATEMENTS

58. In previous scientific studies in this field, pregnant women have given some reasons for their decision to terminate the pregnancy.

Please indicate whether or not these reasons apply to you as well?

Don't think too long, a spontaneous answer will do. These mothers gave the following reasons for terminating their pregnancy:	1. Totally agree 2. Partially agree 3. Undecided 4. Partially disagree 5. Totally disagree				
I think a child with cleft will make me unhappy	1	2	3	4	5
I'm afraid I will regret having a child with cleft	1	2	3	4	5
I'm afraid having a child with cleft will be held against me	1	2	3	4	5
I think that society shows little respect for children with cleft	1	2	3	4	5
I will feel disabled having a child with cleft	1	2	3	4	5
I think the cleft diagnosed is too serious	1	2	3	4	5
I think there is too much insecurity about the consequences of cleft	1	2	3	4	5
I think the cleft will put too much strain on the child itself.	1	2	3	4	5
I comply with my partner's wish to terminate the pregnancy.	1	2	3	4	5

Don't think too long, a spontaneous answer will do. These mothers gave the following reasons for terminating their pregnancy:	1. Totally agree 2. Partially agree 3. Undecided 4. Partially disagree 5. Totally disagree				
I think there will be too much strain on myself	1	2	3	4	5
I think it will interfere with my career/job	1	2	3	4	5
I think there will be too much strain on my relationship	1	2	3	4	5
I think there will be too much strain on my other child(ren)	1	2	3	4	5
I think there will be too much financial strain	1	2	3	4	5

FINALLY, A FEW QUESTIONS ABOUT YOUR PARTICIPATION IN THIS STUDY.
Have you missed certain items in this questionnaire? If yes, please indicate which.
.....
.....
.....
.....
.....
.....

10

Professional counseling after detection of oral cleft. Defending shared-decision making

Submitted

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ABSTRACT

Since the introduction of a more detailed fetal ultrasound, not only severe but all sorts of less severe abnormalities such as oral cleft (OC) are identified. Consequently, prenatal counseling is not only the domain of clinical geneticists and obstetricians anymore, the pediatric surgeon is involved nowadays. Although genetic counseling during pregnancy was generally supposed to be non-directive, there is no consensus concerning the most appropriate type of counseling in case of oral cleft. This debate explores three types of counseling: non-directive, shared decision making, and paternalistic counseling. Elaborating the pro- and contra arguments for these types of counseling can provide physicians with the insight on the ethical background and guide them in the handling of this practical dilemma.

INTRODUCTION

Current prenatal screening, in general, includes a first trimester risk assessment for the most common aneuploidies and a second trimester ultrasound (US) to identify fetal anomalies. Whereas screening was developed to inform prospective parents and give them the choice of continuation or termination of pregnancy in case of a limited number of abnormalities, the unavoidable trend – stimulated by technical advancement and ever improving US - is towards more detailed screening [1], leading to an increased detection of all sorts of less severe abnormalities and discussions about termination of pregnancy (TOP) for those abnormalities. Oral clefts (OCs) are amongst the most common congenital malformations in humans and arise in approximately 1 of 700 live births [2] with a prenatal US detection rate of 88% [3].

> Case description: Mr. and Mrs. de Jong (32 and 30 years old, respectively) undergo routine prenatal US at 20 weeks of gestation, when a cleft lip and palate is detected. Not prepared for detection of an abnormality they are shocked. They have heard vaguely of oral cleft before and Mr. de Jong recalls an old classmate with a scar of his upper lip and speaking weirdly. The midwife assessing the US does not know much about oral cleft, but arranges referral to the special prenatal clinic of the Wilhelmina's Children Hospital. Searching the Internet the parents find all sorts of pictures, differing from an awful looking baby to a perfectly normal looking operated child. In doubt concerning the prospect of their future child they consider termination of pregnancy.

The finding of a facial malformation on prenatal ultrasound can be a major psychosocial burden for parents, who may express signs of severe distress [5,4]. Nevertheless, non-syndromic oral clefts are nonlethal birth defects and most have an excellent functional and aesthetic prognosis once accurately treated. In the Netherlands a minority of the parents considers termination of pregnancy (TOP) in case an OC is detected (Maarse and others, submitted) [6]. In other countries as Israel, the TOP rate for OC is higher [7]. Consequently the use of prenatal diagnosis raises important ethical issues, for both parents and physicians. Prospective parents, in case they consider TOP, need to decide

in a very short period of time (before 24 weeks of gestation). Physicians, responsible for prenatal care, have to determine their tone of counseling.

Before the introduction of prenatal US, parents were usually confronted with OC at birth. Because of increased prenatal detection rates [3], cleft lip and palate teams should participate in prenatal counseling. In our hospital in Utrecht, the Netherlands, we have set up a specialized clinic to participate in the counseling of prospective parents. In such a clinic an obstetrician together with a plastic surgeon and a psychologist perform counseling. They provide information concerning prognosis, treatment, and psychosocial morbidity. We previously (Maarse et al. submitted) demonstrated that prospective parents were very satisfied concerning this type of counseling. In addition, this study showed that physicians have significant influence on parents' opinion concerning the expected burden of an OC. In a different study, it was found that obstetricians perceive OC as a more serious condition in comparison to prospective parents [8]. All together this stresses the possible influence of professionals in the counseling process of prospective parents, especially in those cases when prospective parents consider TOP.

The involvement of pediatric surgeons in counseling during the prenatal phase is a relatively new phenomenon [9]. Surgeons are inclined to provide "best-practice advise" to the patient [10], and are actors of a more direct approach in daily practice. Cleft lip and palate teams struggle with the tone of prenatal counseling (Maarse and others. submitted). The main concern of those teams is to provide sufficient and complete information, and to allow prospective parents to make an informed decision and to respect and protect parental autonomy [11]. Elements considered to be a necessary condition for autonomous decision-making are: the presence of valuable options, clear information about the alternatives and the absence of guiding influences [13, 12, 15, 14]. The question is how can we determine which type of counseling is most appropriate? We provide in this paper an overview of historic and current types of counseling, including their pros and cons as found in the literature, based on which we suggest what form of counseling is best justifiable.

DIFFERENT TYPES OF COUNSELING

Non-directive counseling

Non-directive counseling is comparable to the informative model of Emanuel and Emanuel [16], in which the physician provides all the facts, hence provides no advice and there is only a role for the patient's values. The physician is the purveyor of technical expertise and the active conception of patient autonomy is patient control over medical decision-making without any pressure from the counsellor. This means that 'the counselor does not direct the decision-making process, but only provides all the information needed for making an informed-decision' [17].

Shared decision making

In shared decision making, health professionals and patients are partners in making difficult decisions [18]. Some argue that respect for autonomy does not require the patient to make a decision alone and unaided [19]. Being autonomous encompasses the freedom to delegate the decision to others, to look for help and even to be influenced by others. Shared decision-making concerns a range of approaches, specifically the interpretive and deliberative model of Emanuel and Emanuel [16]. Both aim to assist in articulating patient's values, determine what he or she actually wants, and to select the available medical interventions that realize these values. The level of involvement of the physician may vary, from working with the patient to elucidate his or her values, to suggesting or getting involved in determining which health values are more valuable. Importantly, the physician does not dictate the patient; it is the patient who ultimately decides which course of action is best. In these models the physician is an advisor or a friend, a teacher. Accordingly the active conception of patient autonomy is a relational one in which self-understanding and moral self-development play an important role [16].

Paternalistic counseling

In this type of counseling the physician uses his or her skills to determine what is best for the patient, predominantly from a medical perspective, and hence presents only selected information. In the paternalistic model of Emanuel and Emanuel (Emanuel and Emanuel 1992), the physician acts as the patient's guardian. The active conception

of patient autonomy is assent; the physician decides what is best for the patient, who can only confirm the option presented to him.

DISCUSSION OF THREE MODELS

Arguments given in favor of non-directive counseling

According to Emanuel and Emanuel (Emanuel and Emanuel 1992), in non-directive counseling there is a high level of patient autonomy, understood in its liberal way. Individuals are best placed to judge themselves how to pursue the perception of good (Mill 1978), or in other words to choose what is best for them. Also in the context of prenatal screening, reproductive choices should be personal (Hertig and others 2014). The physician should only provide facts and the patient is the one who should value this information and make a decision (Bolt 1997).

Objections to non-directive counseling

Non-directive counseling is supposed to create an emotional distance between the physician and the patient (Williams and others 2002) and there is no caring approach, because this implies understanding of patient values (Emanuel and Emanuel 1992). Moreover it withholds essential qualities of the physician, namely their experience. In other words non-directive counseling reduces the role of the physician to that of a technologist, which is not the essence of doctoring (Emanuel and Emanuel 1992). Also it supposes that a person possesses known and fixed values, whereas people are often uncertain about what they want(Emanuel and Emanuel 1992) and additionally they are emotional and unable to make a rational decision in such a short period of time after detection of a malformation (Caplan 2014). Some authors argue that objective information in counseling is not possible (Bolt 1997). Counseling can't be value neutral and a truly non-directive counseling is rarely observed in daily practice [22]. Furthermore a non-directive approach may seem confusing for patients who are used to physicians who give their opinion [10]. Even worse, patients can feel guilty, uncertain and angry when no recommendations are given [23].

Arguments in favor of shared decision making

"Autonomy means that a person is able to relate to him- or herself and to others in both a critically reasoned way and his or her way", in essence you relate to opinions and advice of others" [22]. In shared decision making the physician assists the patient in articulating his or her values, so that he or she realizes what is best for them. Patients' values are not fixed [16]. Kuitert argues that a patient needs assistance to become an autonomous individual by helping the patient to understand; a person is autonomous when he or she can give good reasons for her or his choices [24]. So providing only information is not enough to support those concerned in making a good choice. Shared decision making might allow patients to consider implications they might not have thought about and gain insight into the consequences of certain choices.

Objections to shared decision making

For shared decision making, the physician has to gain insight into patient's values and relate these to his or her own values. It can be argued that the values of physicians should not be involved here [16]. Furthermore it seems rather difficult to gain insight into patients' values in such limited time during prenatal consultation. Also a patient and physician do not always have to agree, which cannot only undermine their relationship, it can also change the tone of counseling when parents and patients perceive the burden of an anomaly differently [25]. Finally there is a risk that physicians withhold information because of fear or anxiety of patients, or because they think the patient has low emotional intelligence [10]. Physicians can easily channel parents into a decision that they feel is correct, whereas they are actually manipulative [26].

Arguments in favor of paternalistic counseling

Some argue that physicians have unique knowledge and experience with certain abnormalities and consequently know what therapy benefits the patient's values [16]. According to Conly [27] this approach is not paternalistic but instead a projection of what is good, based not on physician values, but upon expertise and experience. Patients will never be perfectly rational (and will be overwhelmed after discovering they will not have a "perfect baby") and their values do not line up in a neat and orderly fashion, in other words they need a little 'paternalistic help'. Levy [28] argues "the

picture of a rational individual that underlies the doctrine of informed consent is not psychologically realistic: we cannot expect patients to take on so much of the burden of making choices that will advance their own significant interests. Mild coercion will not just improve the quality of the decision, but it will also increase autonomy " [28]. To conclude, Levy believes that there is bias in how patients judge information and that this will reduce their quality of decision making, in contrast to physicians who are not prejudiced by fear and other motivations.

Objections to paternalistic counseling

Paternalistic counseling can be risky since patients are very easily influenced by physicians [21]. This type of counseling can easily reform into real pressure [28] and even has a risk to drift towards eugenics [22]. In eugenics there is, among other huge problems, a violation of autonomy [22]. In some countries like China, geneticists openly admit that prenatal screening is used as a manner to improve the progeny [26]. This latter practice shows that although physicians have more expertise, their motivations are - similar to patients - never value neutral. Their experience will therefore bias their way of counseling.

DISCUSSION

As the use of routine scanning of the face with US has become standard, prenatal diagnosis of OCs is now common practice. Cleft lip and palate teams are involved in counseling and apparently influence prospective parents' opinion concerning the burden of an OC. Consequently, they have to determine the most appropriate form of counseling. Three types of counseling were described, specifically non-directive, shared decision making and paternalistic counseling.

After exploring the main pro- and contra-arguments of different types of counseling given in the literature, we think a more directive approach than the non-directive one is appropriate. We therefore think shared decision making is the best counseling model in case of OC. We see several reasons for this position. First, prospective parents need help to become autonomous. After diagnosis of an OC they are usually overwhelmed

which is not an ideal period for rational decision-making. Second, if they consider TOP they should decide in a very short period of time because legal regulations which prohibit late termination, at least in the Netherlands. Physicians of the cleft lip and palate team have extensive experience with OC and can therefore empower parents. It can be argued, however, that the plastic surgeon might have self-interest in optimistic counseling, since treating children with OC is his or her daily work. However the majority of children with OC have normal intelligence so counseling is not optimistic, but rather realistic. Third, "getting more involved" in counseling expresses a more caring approach: "you take some of the burden from them" [21] and reduce their anxiety [29, 9]. Prospective parents can feel that they are supported and realize they are not alone in raising a child with a condition hitherto unknown to them. A more directive attitude is also appropriate because it enables parents to gain insight into specific motives and into the meaning of a particular choice [22]; to get there it is sometimes necessary for physicians to express opinions and give recommendations. This approach aids parents to ultimately critically assess their own values and preferences, which in turn leads to (good) personal choice making. Finally, it can be argued that in developed countries treatment of children with OC is generally excellent, due to good health care facilities and adequate medical insurance, which implies there is really also a benefit to be gained.

Implications for clinical practice

To argue for shared decision making in the counseling practice of OC, influences not only the counseling as such, but also the organization of the prenatal care path. In order to provide for the interactions that constitute shared decision making, a few elements are needed; fast referral by the midwife or obstetrician after detection to a multidisciplinary team containing not only specialists in surgical treatment of OC, but also in psychological care. Moreover there should be ample time reserved for counseling. The specialist of the cleft lip and palate team is, contrary to the obstetrician, the one who takes care of the baby after birth. The parents will feel more trusting when discussing with the doctor who will try to correct the malformation and who will follow up their child long term, until adolescence or even beyond.

CONCLUSION

We propose that professionals in prenatal counseling after OC is diagnosed, take a more directive approach as in shared decision. This has implications both for the direct interaction as for the organization of the prenatal care path of OC. Good care in this respect is contributing to parents becoming autonomous. However, this does not mean that professionals should dictate parents. In this approach parents are able to ultimately judge for themselves the expected impact of OC on their prospective child and family and make their own decisions.

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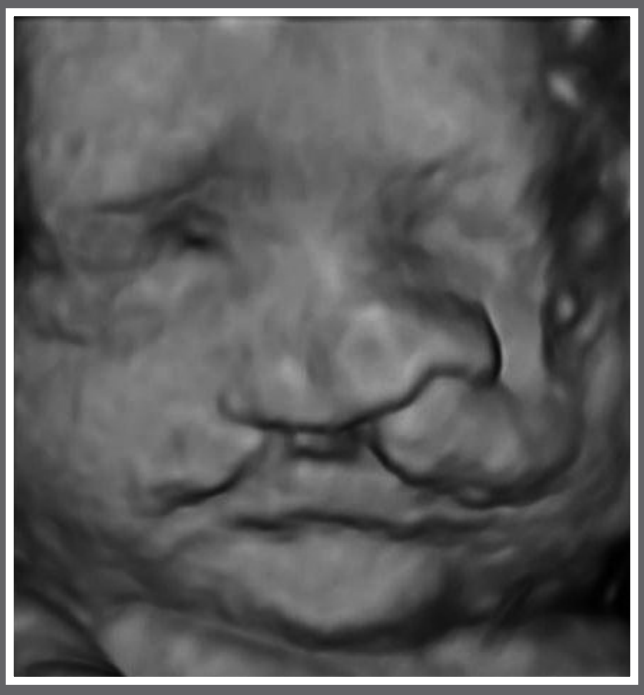

Part IV
Discussion and Summary

11

General discussion and future perspectives

Since the introduction of routine prenatal screening with ultrasound in the Netherlands in 2007, parents are confronted with the diagnosis of oral cleft (OC) already during pregnancy[1]. This imposed a new dimension in cleft care in the Netherlands. As a consequence to increasing prenatal detection rates, the cleft lip and palate team of the Wilhelmina Children's Hospital in Utrecht set up a multidisciplinary prenatal cleft clinic in which a plastic surgeon, an obstetrician, medical psychologist and clinical geneticist together facilitate in counseling. Although the diagnosis of OC prenatally and related counseling results in better education and preparation before birth, it also poses a significant ethical dilemma. Even though cleft lip and palate teams in the Netherlands can provide excellent care, there is concern that fewer children with OC will be born due to TOP in the near future as a result of prenatal screening. The latter inspired us for the start of this thesis.

In order to improve counseling we needed accurate information. In the first part of this thesis we assessed the different types of OC that can be detected by screening. Furthermore we evaluated the accuracy of detection of OC, the association with other anomalies and the role of invasive genetic tests. The second part of the thesis faces the prenatal counseling process of OC itself. We evaluated the opinion and attitude of both professionals and prospective parents on OC, the expected burden of OC and their opinion about TOP. Finally in the last part, we discussed the ethical background of counseling and argued which type of counseling is most appropriate in case of OC. Below, these two parts of this thesis will be discussed separately under the headings of accuracy of screening for OC and prenatal counseling.

ACCURACY OF SCREENING FOR ORAL CLEFT

In **chapter 3** we explained the emergence of prenatal screening of OC in the Netherlands. Suitably in **chapter 4** we showed, in a systematic review, the large variety in diagnostic accuracy of detection of OC by US. With detection rates described in this review, ranging from 0-75%, counseling seemed difficult. However since the start of routine screening in the Netherlands at 20 weeks of gestation, prenatal

ultrasound (US) has become a uniform process. This allowed us to start a prospective study to assess the quality of detection by US (**chapter 5**), which demonstrated a much higher accuracy of detection of OC by current US techniques in comparison to former studies. However, isolated cleft palate was rarely diagnosed and in those cases where a cleft lip was suspected, the incidence of an additional cleft palate was often underestimated (i.e. false negative). Somehow, the detection of a cleft palate remains difficult; a former US classification did not even include an isolated cleft palate as a separate type[2]. In recent years several studies aimed to improve the detection of cleft palate by introducing new sonographic techniques[3]. One of these techniques, the appearance of an 'equal sign'[4], is currently used in our clinic. This marker refers to a normal uvula. Since we understand from embryology that the palate closes from anterior to posterior, an unremarkable uvula thus implies the presence of an intact palate. The introduction of this technique is a plausible explanation for the few cases of isolated cleft palate detected in our prenatal clinic in comparison to none at all before introduction in 2011. Moreover, in **chapter 6** we observed increased accuracy in classifying the type of OC over time. However, the equal sign is not yet reliable enough; even when a cleft lip is diagnosed there is a fair chance of missing the additional cleft palate as we showed in **chapter 2**. Also two recent studies[14, 15] showed the same number of misdiagnoses (approximately 30%) when compared to accuracy in determining the type of OC in our studies. This had mainly to do with missing the additional cleft palate. The latter has clinical implications since cleft palate is often associated with difficulties in speech[5], feeding[6], hearing[7] and mid-facial protrusion[8]. Isolated cleft palate represents approximately one-third of all OC[9]. Therefore, we proposed isolated cleft palate to be included in prenatal classification systems. A reliable and reproducible classification of prenatal OC, as we presented in **chapter 2**, is essential because an accurate diagnosis is a prerequisite for informing prospective parents adequately on the prognosis and outcome. Furthermore different types of cleft are variably related to specific risks of associated anomalies, as we showed in **chapter 7**. We discovered that the presence of other congenital anomalies on US, in combination with OC is a strong predictor for chromosomal defects. Therefore, we proposed that additional genetic counseling should be offered to those women in whom associated anomalies are observed, irrespective of cleft category. One should

realize however, that absence of associated anomalies does not preclude the presence of underlying chromosomal defects. Based on our algorithm discussed in **chapter 7**, parents should be routinely advised to consider consultation of a geneticist and invasive testing in case of cleft lip ± palate and isolated cleft palate. When considering invasive testing the baseline risk on complications hereof (<1%) should be outweighed by the potential benefits[10, 11]. Another concern that should be discussed with parents is the possible detection of unexpected or unclassified variants of chromosomal defects with array based methods[12, 13]. In conclusion, we showed an unambiguous evidence that different cleft categories can be associated with a variety of additional congenital anomalies and underlying chromosomal defects. This emphasizes the need for an accurate classification of OC to be used in US screening.

Implications for further research

To improve the diagnostic precision of current OC classification it is mainly important to improve the visualization of the palate, as outlined above. The new prenatal US classification system presented in this thesis can provide a systematic and practical approach for prenatal screening. Additionally, implementation of new techniques, like the 'equal sign'[4] or three-dimensional reverse-face view[16] and improving the training of sonographers could be beneficial to improve the accuracy in diagnosis OC.

In the Netherlands, the vast majority of anomalies associated with an OC are detected with US. However, it is important to be aware of the chance of additional (later) medical or developmental issues in an apparently isolated OC. The latter is especially relevant since the identification of isolated cases of OC is increasing (**chapter 4**). First, prospective studies with longer follow-up are needed to gain more insight in minor abnormalities and syndromes that generally become more evident later in life, such as the 22q11.2 deletion syndrome[17]. Second, technological advancement in genetics is moving quickly, thereby improving the ability to analyze the human genome faster and at lower cost. As a result, the use of next generation sequencing is expected to be implemented in the near future.

Future perspectives

The role of invasive prenatal testing could change completely with the introduction of another technical innovation, the so-called non-invasive prenatal testing (NIPT). NIPT, refers to cell-free fetal DNA-based tests in maternal plasma[20, 21] that can be performed as early as after 7 weeks of pregnancy[22]. The main advantage of this test is that the procedure-related miscarriages of invasive techniques are avoided since NIPT requires only blood samples from the mother. Current prenatal screening in the Netherlands includes a first-trimester risk assessment for the most common aneuploides and a second-trimester fetal ultrasound to identify fetal anomalies[18]. In case of a positive risk assessment, invasive procedures are offered. However, based on the advice of the Dutch Health Council[19] in December 2013, ministerial permission was granted to perform NIPT as the first follow-up test if the combined test indicates an increased risk of trisomy. Although NIPT seems a more reliable screening test for common aneuploidies when compared to the combined test, at this point NIPT alone is not yet recommended as an routine alternative due to the lack of research results in the general population[21]. If NIPT becomes the test of first choice, the combination test may no longer be needed, implying that nuchal translucency measurement by US as part of the combined test may no longer be performed in the near future[23]. A different advantage of NIPT, although currently not in its scope, is the fact that subchromosomal abnormalities, such as 22q11 deletion[24] can also be detected. This might influence the number of children born with an associated OC, since NIPT is performed in an early stage of pregnancy thereby possibly influencing the decision to terminate the pregnancy. Nonetheless, ultrasounds screening around 20 weeks of gestation will probably remain part of routine screening because it was introduced to screen for observable structural anomalies, which are not detectable by NIPT. Therefore, it is expected that the detection of "truly" isolated OC after a negative NIPT test by US around 20 weeks of gestation will remain part of our clinical reality.

PRENATAL COUNSELING

In **chapter 9** we prospectively analyzed thoughts and attitudes of parents expecting a child with OC. The findings demonstrated the opposite to the concerns put forward in literature; namely that the prenatal diagnosis of OC would lead to an increase of TOP[27, 28]. We found that most future parents in the Netherlands believe that an isolated OC is a cosmetic disability or "just a little different". Thus most parents do not even consider TOP. Other studies demonstrated a more serious expected burden of OC and hence an increased fear of stigmatization. Such parents perceived the defect as severe[30, 31], feared for the intelligence of the child[32] and were anxious about the child's self-esteem and -image[33]. In the literature there are striking differences among countries with respect to TOP rates for OC, with fairly high rates in countries like Israel[28] and rather low rates in the Netherlands (**chapter 9**). It is possible that the perceived burden of OCs in those countries is higher, which would be an explanation for higher rates of TOP for isolated OC. In **chapter 8** we found that the opinion about OC of the professional also did not explain the dramatic difference in TOP between Israel and the Netherlands; they did not differ significantly in their judgment on the severity of OC and the acceptability of TOP. In the literature a variety of other factors are suggested to be responsible for the differences, such as religious, legal, social, cultural, financial circumstances, gestational age at diagnosis besides the expected burden of OC[29]. In addition, it not always clear how the prenatal care path of a fetus with an OC is organized in these countries nor is it known if and how counseling is performed.

Furthermore, in **chapter 9** we found that health care professionals have significant influence on the parents' perception of thoughts regarding OCs, particularly by the obstetrician and plastic surgeon of the cleft lip and palate team. Other studies confirmed that perception of the severity of certain conditions are mediated by the care provider's counseling[34-36]. In **chapter 8** we found that obstetricians in the Netherlands perceive OC as a disability, in contrast to prospective parents who think of OC as a cosmetic disability. The cleft lip and palate team should be aware of these differences. Given the fact that most prospective parents did not even consider TOP when an isolated OC was detected, TOP is not always discussed during counseling in our hospital. The most important goal of counseling by the cleft lip and palate team is to give extensive

information. Nevertheless, the cleft lip and palate team should be aware of the tone of counseling. In **chapter 10** we therefore provided an overview of different types of counseling, including their pros and cons as put forward in literature. It was concluded that a more directive approach of counseling is appropriate and contributes to prospective parents becoming autonomous. They are usually overwhelmed and need help to understand their own values and preferences concerning OC. Also in a more directive counseling the health professionals expresses a more caring approach, "you take some of the burden for them"[39]. Prospective parents feel that they are supported and realize they are not alone in raising a child with a, to them hitherto unknown condition. This approach is different from counseling for more severe conditions for which prenatal screening was originally designed. The main aim of prenatal screening for aneuploidies is 'to provide meaningful reproductive choices' to the pregnant woman and her partner[19], implying that screening for abnormalities may lead to an informed decision to terminate the pregnancy. However, the detection of OC was not part of the original screening program; it was an unintended consequence of a standard US at 20 weeks of gestation. Hence, it may be justified to have non-directive counseling in case of aneuploidy, but in case of OC we have argued for a more directive approach.

Implications for clinical practice

As was shown in our study in **chapter 9** prospective parents are in need of professional support after discovering their future child has an OC. This stresses the importance of a uniform organization of prenatal OC care. In 2011 a multidisciplinary guideline[25, 26] initiated by the Dutch Association of Plastic Surgery was published. This guideline stated that referral after detection of OC should be realized within a week, meaning that tertiary US centers should closely collaborate with local cleft lip and palate teams. In addition it was proposed that counseling should be preferable be done by two members of the team together, of which one has knowledge of the (surgical) treatment and the other covers the psychosocial aspects of having a child with an OC. In the Wilhelmina Children's Hospital prenatal counseling is indeed a team effort and is conducted on a regular basis. Once referred, the obstetrician repeats an anomaly scan in the presence of the partner, the plastic surgeon and the medical psychologist. Ample time is reserved directly thereafter for prenatal counseling by the team. The

three-dimensional view allows the plastic surgeon to tailor prenatal counseling to the exact OC type, including its severity and anticipated postnatal management. In **chapter 9** it was also confirmed that prospective parents were satisfied about this way of counseling and active involvement of the cleft lip and palate team was concluded to be extremely helpful. Not only the counseling as such, but also the organization of our prenatal oral cleft path contains already elements of directive counseling as we explained in **chapter 10**. The members of the cleft lip and palate team are after all, in contrast to the obstetrician, the ones who take care of the baby after birth. Parents will probably feel more comfortable when discussing with the doctor who will treat the malformation and will perform long-term follow-up of the child. However, as stated before, it remains unknown how uniform this process of referral and counseling is in other regions in the Netherlands, let alone in other countries.

Implications for further research

In this thesis we performed the first prospective study to assess the thoughts and attitude of parents expecting a child with OC. Inclusion was however after counseling. To assess the influence of counseling by the cleft lip and palate team itself, prospective parents should be interviewed or surveyed both before and directly after counseling in a new study. Furthermore to identify other factors that may influence parents' decisions regarding whether to choose TOP when an (associated) OC is diagnosed, a comparative study would need to be carried out in two populations, one in which TOP for OC is rare and one in which TOP is common.

CONCLUSIONS

In this thesis we provided more insight into a new care path, namely the path after prenatal detection of OC. We showed that the detection of OC by ultrasound is accurate and we expect it only to increase. We hope that better understanding of embryology and the new classification helps to improve further distinction between different types of cleft, because this is very relevant for the probability of finding additional anomalies as well as for prognosis and treatment. Furthermore accurate

prediction of the type of OC is important for the expectant burden and with greater accuracy we can provide more balanced counseling. Although this thesis showed that the majority of prospective parents don't consider termination of pregnancy in case of oral cleft, we cannot predict the influence of NIPT, which possibly leads to even earlier detection of associated OC. It remains a challenge for us, as plastic surgeons of cleft lip and palate teams, to be actively involved in counseling and continue to be an integral part of this care path.

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12

English summary

Dutch summary/Nederlandse samenvatting

SUMMARY

Since the introduction of standard prenatal screening in the Netherlands by means of ultrasound in 2007, parents are confronted with a child with an oral cleft already during pregnancy. As a response, some cleft lip and palate teams have set up a specialized prenatal cleft clinic to participate in the counseling of pregnant women. The aim of this study was to investigate different factors of prenatal detection of oral cleft, in order to improve prenatal counseling. Primarily, counseling is important to inform parents about the medical aspects of oral cleft. Since this thesis focusses on only the prenatal aspects of oral cleft, in **chapter 1** we provide a state of the art overview on epidemiology, embryology, pathophysiology and treatment. Oral cleft is a congenital malformation that can involve the lip, palate, nose and underlying bony fragments in various severities, and is the most common craniofacial anomaly considering an incidence of approximately 1:700 births. Oral cleft is a result of failure of both growth and fusion of the face, which is established between the 4th and 10th week of human development. Besides the aesthetic complication of oral cleft there are functional problems related to the abnormal anatomy. In brief, speech can be complicated due to velopharyngeal insufficiency, there can be hearing disability, feeding difficulties and dentofacial deformities. A multidisciplinary approach is essential for satisfactory treatment of cleft patients. Surgical correction consist of reconstruction of a symmetrically balanced lip and nose and an intact and functional palate to optimize speech. The course of treatment spans often the entire childhood and although the primary management is surgically driven, the overall goal of treatment includes also a psychosocial wellbeing of the patient and his or her family. Prenatal detection of oral cleft has added a new dimension to the above described cleft care.

Part I Classification of Oral Cleft

Since introduction of screening for fetal anomalies, ultrasonographers are challenged to diagnose not only an oral cleft, but moreover the precise type of oral cleft. Accurate diagnosis is essential because it correlates with the severity of the malformation, and different treatment and prognosis. In **chapter 2**, a new prenatal oral cleft classification is defined using a practical approach that could be easily applied in ultrasound

practice. During a three-year period (2011-2014), all cases of oral cleft diagnosed by ultrasound where retrospectively reviewed, which resulted in a total of 103 fetuses. For the purpose of validation prenatal images were compared to postnatal findings. The measurement of agreement between these pre- and postnatal findings showed a Kappa value of 0.63 (95% CI: 0.52-0.75), demonstrating the accuracy of this new classification system.

Part II Screening for Oral Cleft

In **chapter 3**, the history and background of screening for fetal anomalies, with a focus on oral cleft is presented. A countrywide routine screening, initially only for Down syndrome and neural tube defects, but later also for oral cleft, was introduced by legislation in 2007. The Netherlands were quite late in setting rules for this field. Routine screening was postponed because the Ministry of Health, Welfare and Sport defended the view that possibilities for prenatal treatment and prevention were minimal. After legislation, equal access and standard coverage by health care insurance was ensured. The screening is thus primarily to inform future parents about a possible defect and about their postnatal treatment options. Informed consent, after being educated about potential implications of screening and the right not to know, is mandatory. In order to reduce costs and ensure easy access, basic screening takes places at primary care level, by certified midwives and sonologists. In case of a suspected abnormality the women is referred to a certified obstetrician in one of eight regional referral centers, who performs more detailed screening. Except when very severe anomalies, such as trisomy 13 or 18 are identified, the cleft lip and palate team is routinely consulted in the region of Utrecht. In this special set up prenatal clinic the obstetrician repeats the scan in the presence of the plastic surgeon, after which counseling takes place by both the plastic surgeon and medical psychologist of the team, so that parents are well prepared. Due to more ultrasound screening, there is an increase of second term pregnancy terminations, although data from Utrecht show a very low termination rate for isolated clefts. To establish a uniform counseling process in case an oral cleft is detected, a national multidisciplinary evidence-based guideline was initiated.

Chapters 4, 5 and 6 all assess the diagnostic accuracy of ultrasound screening of oral cleft. A systematic review (**chapter 4**), covering all articles published before 2008, showed considerable variety in accuracy of two-dimensional ultrasound in low-risk women (unselected population based studies), with detection rates ranging from 9% to 100% for cleft lip with- or without cleft palate, 0% to 22% for cleft palate only and 0% to 73% for all types of cleft. There were only few false-positive cases. In general the methodology was of poor quality and subsequently the review provides the sources of variability and suggestions for further research. **Chapter 5** revealed the results of a prospective study, in which all pregnant women who underwent routine second-trimester screening in the Utrecht region during the 2-year period from January 2007 to December 2008. There were 62 cases of oral cleft, providing an incidence of 1: 624. The distribution of clefts was as follows: 18 (29%) cleft lip (CL), 25 (40%) cleft lip with cleft palate (CLP), 17 (27%) cleft palate only (CP), one median cleft and one atypical cleft. Of these, 38 (61%) were unilateral and 23 (37%) were bilateral. Thirty-nine per cent (24/62) had associated anomalies, with most chromosomal defects found in the CLP and CP groups. Cleft lip with or without cleft palate (CL ± P) was detected prenatally in 38/43 cases, a sensitivity of 88%. No case of CP was detected prenatally. There were three false- positive cases, of which two were fetuses with multiple congenital deformities. In conclusion there was a high sensitivity for the detection of CL ± P in our region. The key to a high sensitivity of prenatal ultrasound is likely to be a combination of excellent training of sonographers, referral to specialized centers when a cleft is suspected, routine visualization of the fetal face and advances in ultrasound techniques. In **chapter 6** we aimed to determine the accuracy of ultrasound in assessing the type of cleft. Prenatal diagnosis was in accordance with postnatal findings in 76.9% of cases (103/134) with regard to the cleft type. Underestimation of the cleft occurred in 19.4% (26/134), whereas in 3.7% (5/134) the extent of the cleft was overestimated. In distinguishing bilateral from unilateral clefts, no errors were made. These results indicated that prenatal ultrasound is a reliable technique to assess the cleft type, which is important in counseling future parents. Although, the clinician should be aware of the fact that a cleft palate is easily missed, and subsequently underestimation of cleft severity is frequent. This study served as basis for developing a new classification, described in chapter 2.

When informing parents on outcome and prognosis, not only the cleft type but also the risk of associated anomalies is crucial. In particular the presence of an underlying chromosomal defect will influence prenatal counseling and management. In **chapter 7** on overview is given on associated anomalies and chromosomal defects in oral clefts. Data from the literature were completed with validated data from the Dutch Oral Cleft Registry. The pre- and postnatal studies showed that the prevalence of associated anomalies was lowest in CL (0–20.0% and 7.6–41.4%, respectively). For CLP, higher frequencies were found both prenatally (39.1–66.0%) and postnatally (21.1–61.2%). Although CP was barely detectable by ultrasound, it was the category most frequently associated with accompanying defects in postnatal studies (22.2–78.3%). Chromosomal abnormalities were most frequently seen in association with additional anomalies. In the absence of associated anomalies, chromosomal defects were found prenatally in CLP (3.9%) and postnatally in CL (1.8%, 22q11.2 deletions only), CLP (1.0%) and CP (1.6%). This systematic review showed that prenatal counselling regarding prognosis and risk of chromosomal defects should be tailored to cleft category, and more importantly to the presence or absence of associated anomalies. Irrespective of cleft category, clinicians should advise invasive genetic testing if associated anomalies are seen prenatally. In the absence of associated anomalies, prenatal conventional karyotyping was not recommended in CL, although array comparative genomic hybridisation should be considered. In presumed isolated CLP or CP, prenatal invasive testing, preferably by array-based methods, was recommended.

Part III Prenatal Counseling

Since this thesis aimed to improve prenatal counseling for oral cleft, we made an effort to identify different factors which are thought to influence parental opinion on oral cleft, one of them being the obstetric care provider's attitude. In **chapter 8** providers' opinions about pregnancy termination for isolated oral cleft were compared in the Netherlands, where the number of terminations is low, and in Israel, where the number is high. Online questionnaires were used. The questions assessed the providers' views regarding the estimated burden of treatment, the functioning ability and the level of happiness of children with an oral cleft and their parents. Additionally, we assessed providers' opinions on pregnancy termination for isolated oral cleft. In the Netherlands,

more professionals considered oral cleft a disability [rate differences (RD) 17.8%, 95% CI: 0.5-33.1%] than in Israel. In the Netherlands, 10.6% of respondents (compared with 11.1% in Israel) thought that an isolated cleft was a reason for TOP [RD 0.6%, 95% CI: -12-10.9%]. In conclusion prenatal care providers between two countries do not differ in their opinions about the severity of oral cleft and the acceptability of TOP for an isolated oral cleft. This study shows that prenatal care providers' attitudes do therefore not explain the dramatic difference between these countries in the number of TOP for isolated oral cleft. In **chapter 9** we analyzed considerations of prospective parents concerning OCs, the burden of OCs and parents' attitude toward possible TOP to improve counseling in the future. Between August 2011 and August 2014, a prospective cohort questionnaire study was administered with parents visiting our prenatal clinic. Most of the parents described an oral cleft as a cosmetic disability (43.6%) or as "just a little different" (26.6%). These parents expected that the OC would not affect their own happiness or the happiness of their future child. Health professionals had a considerable influence on parental opinion. A minority (6.4%, 5/85) of the respondents considered TOP, and none of the participants chose to terminate the pregnancy. The estimated severity of the oral cleft and the estimated influence on the child's happiness both had a significant influence on whether TOP was considered (p=0.04). This study suggests that the active involvement of cleft lip and palate teams is worthwhile. Caregivers should be aware that their counseling is important in the decision making of parents. **Chapter 8 and 9** show that parents and health care professionals perceive the expected burden of cleft differently. Moreover it was assessed that health care professionals had significant influence on the parents' perceived thoughts regarding OCs. All together this stresses the influence of professionals in counseling prospective parents, especially when considering TOP. How can we determine whether and when a more directive attitude of the counselor is justified? In **Chapter 10** three types of counseling are explored: informative, shared decision making, and paternalistic counseling. Elaborating the pro- and contra arguments for these types of counseling can provide physicians insight on the ethical background of this practical dilemma.

In conclusion this thesis provides more insight into a new dimension of cleft care, namely the prenatal detection. When counseling expectant parents on impact of OC, several topics should be reviewed, including postnatal management like feeding, surgical and supporting treatment options, cosmetic outcomes and risk for speech and hearing difficulties, which are all related to specific types of cleft. Classification and accurate diagnosis is therefore of upmost importance. Additionally parents would like to know about the increased risk of additional malformations. This information will determine their expected burden of OC and their attitude towards possible termination the pregnancy. This thesis will help improving not only the information given with counseling, but also help to determine the tone of counseling for OC.

NEDERLANDSE SAMENVATTING

In 2007 is het Structureel Echografisch Onderzoek (SEO), ofwel de 20 wekenecho, toegevoegd aan de prenatale zorgstandaard voor zwangere vrouwen in Nederland. Dit had implicaties voor de prenatale detectie en zorgpad van schisis, die daarvoor vaak pas na de geboorte werd ontdekt. Als reactie hierop hebben sommige schisisteams in Nederland een speciaal prenataal schisisspreekuur opgezet met als doel de counseling van de zwangere vrouw en haar partner die een kindje met een schisis verwachten. Het doel van dit onderzoek is om de verschillende aspecten rondom de prenatale detectie van schisis te onderzoeken, om op deze manier uiteindelijk de counseling te verbeteren. Omdat het onderzoek zich alleen richt op de prenatale kant van schisis, is in **hoofdstuk 1** een overzicht gegeven van de epidemiologie, embryologie, pathosfysiologie en behandeling van schisis. Op die manier kan beter worden ingeschat wat de impact is van een schisis voor de ouders en het kind.

Schisis is een congenitale malformatie waarbij de lip, het palatum, de neus en het onderliggende bot en kraakbeen in verschillende vorm kunnen zijn aangedaan. Het is de meest voorkomende craniofaciale afwijking en heeft een incidentie van 1:700 nieuwgeborenen. Schisis ontstaat door het van falen van groei en fusie in de embryonale ontwikkeling van het aangezicht, tussen de 4^{e} en de 10^{e} week van de zwangerschap. Door de afwijkende anatomie bij een schisis zijn er niet alleen cosmetische, maar ook functionele gevolgen; de spraak kan aangedaan zijn ten gevolge van velopharyngeale insufficiëntie, er kunnen oorproblemen, voedingsproblemen en dentofaciale afwijkingen voorkomen bij kinderen met een schisis. Een multidisciplinaire aanpak is essentieel voor een goede behandeling van kinderen met schisis. De chirurgische behandeling bestaat uit reconstructie van een symmetrisch gebalanceerde lip en neus en een intact palatum voor goede spraak. De behandeling beslaat de gehele jeugd en ondanks de primaire focus op chirurgie, is het algemene doel van de behandeling ook het psychosociale welbevinden van de patiënt en zijn of haar familie. Prenatale detectie heeft een nieuwe dimensie toegevoegd aan de hierboven beschreven behandeling van schisis.

Deel 1 Classificatie van schisis

Met de introductie van de prenatale echo en de detectie van foetale afwijkingen, worden echografisten niet alleen geacht om een schisis te detecteren, maar ook om het juiste type schisis in beeld te brengen. Een accurate diagnose is essentieel omdat het correleert met de ernst van de schisis, en tevens een verschillende behandeling en prognose. In **hoofdstuk 2**, wordt een nieuwe, praktische classificatie geïntroduceerd die gemakkelijk in de echopraktijk zou kunnen worden toegepast. Gedurende een periode van drie jaar (2011-2014), werden alle kinderen met een prenatale schisis retrospectief onderzocht. Dit resulteerde in 103 casussen van prenataal gediagnosticeerde schisis, die in het kader van het validatie van de classificatie werden vergeleken met de postnatale diagnose. Het niveau van overeenkomst tussen de pre- en postnatale bevinding resulteerde in een Kappa waarde van 0.63 (95% CI: 0.52-0.75). Dat wijst op een accurate classificatie.

Deel 2 Screening van schisis

In **hoofdstuk 3** wordt de achtergrond van de start van prenatale screening naar aangeboren afwijkingen beschreven. In 2007 werd een WBO-vergunning verleend voor de SEO, initieel alleen voor de screening van Down syndroom en spina bifida, maar later ook voor schisis. Na het afgeven van de vergunning werd gelijke toegang gewaarborgd door het opnemen van de SEO in het basispakket van de zorgverzekeraars. In vergelijking met andere Europese landen was Nederland laat met de invoering van een nationale prenatale screening. Het ministerie van Sport, Welzijn en Gezondheid stelde de vergunning eerder uit, omdat de mogelijkheden voor prenatale behandeling en preventie van de aangeboren afwijkingen, normaal gesproken voorwaarden voor screening, minimaal zijn. Primair is de screening dus bedoeld om zwangeren te informeren over de mogelijke aanwezigheid van een aangeboren afwijking en de bijbehorende postnatale behandelopties. Een informed consent voorafgaand aan de prenatale screening, nadat ouders geïnformeerd zijn over de potentiële gevolgen van screening, is verplicht. Om de kosten laag te houden en om een gelijke toegang te garanderen, wordt de SEO verricht door verloskundigen en echografisten in de eerste lijn. Bij een verdenking op een aangeboren afwijking wordt de zwangere vrouw verwezen naar een gespecialiseerde gynaecoloog in één van de acht

Nederlandse verwijscentra. Aldaar wordt een Gespecialiseerd UltrageluidsOnderzoek (GUO) verricht. In Utrecht wordt bij de detectie van een schisis, met uitzondering van zeer ernstige afwijkingen zoals een trisomie 13 of -18, routinematig het schisisteam geconsulteerd. Er is in 2007 een gespecialiseerd prenataal spreekuur gestart, waarbij de gynaecoloog de echo herhaalt in aanwezigheid van de plastisch chirurg. Hierna is er ruimte voor gecombineerde counseling door de plastisch chirurg en de psycholoog van het schisisteam. Op deze manier worden de ouders zo goed mogelijk voorbereid op de komst van een kindje met een schisis. Om uniforme counseling te waarborgen, is door de Nederlandse Vereniging van Plastische Chirurgie (NVCP) het initiatief genomen tot de ontwikkeling van een nationale evidence-based richtlijn. Ten gevolge van een hoger percentage vrouwen dat prenatale screening ondergaat, is er de afgelopen jaren een stijging gesignaleerd van het aantal late zwangerschapsafbrekingen. Het aantal zwangerschapsafbreking voor geïsoleerde schisis in Nederland lijkt daarentegen zeer laag.

In **hoofdstuk 4, 5 en 6** is de nauwkeurigheid van de prenatale echo in de detectie van schisis onderzocht. **Hoofdstuk 4** is een systematic review van alle artikelen die de kwaliteit van de echo in detectie van schisis onderzochten, vòòr 2008. Deze lieten een grote variatie zien in de detectie van schisis in een laag risico populatie. De detectie ratio's varieerden van 9-100% voor schisis van de lip eventueel in combinatie met schisis van het palatum (CL ± P), 0-22% voor schisis van het palatum (CP) en 0-75% voor alle typen schisis. Er waren maar enkele vals-positieve casussen. Over het algemeen was de kwaliteit van de methodologie in deze studies laag en daarom geeft het review een overzicht van potentiële bronnen van variabiliteit en suggesties voor volgend onderzoek.

In **hoofdstuk 5** werden alle vrouwen die een SEO ondergingen in de regio Utrecht gedurende een periode van 2 jaar (2007- 2008) prospectief gevolgd. In deze groep werden 62 kinderen met een schisis geïdentificeerd, wat vertaalde naar een incidentie van 1:624. De verdeling van de verschillende typen schisis was als volgt: 18 (29%) CL, 25 (40%) CLP, 17 (27%) CP, één mediane schisis en één atypische schisis. Hiervan was 38 (61%) unilateraal en 23 (37%) bilateraal. Bij 39% (24/62) was er sprake van één of meerdere bijkomende afwijkingen, waarbij de chromosomale afwijkingen het meest voorkwamen in combinatie met een CL ± P en een CP. CL ± P werd in 38/43 van

de gevallen prenataal gedetecteerd door middel van echo, wat resulteerde in een sensitiviteit van 88%. CP werd geen één keer prenataal gedetecteerd. In drie gevallen was er sprake van een vals positieve bevinding, waarvan er bij twee foetussen sprake was van multipele bijkomende afwijkingen. Concluderend was er sprake van een hoge sensitiviteit in de detectie van prenatale schisis in onze regio. De sleutel naar een hogere sensitiviteit lijkt een combinatie van goede training van de echografisten, verwijzing naar een gespecialiseerd centrum bij een verdenking op een schisis, routine visualisatie van het aangezicht en tot slot technische ontwikkeling van echotechnieken.
In **hoofdstuk 6** hebben we specifiek gekeken naar de nauwkeurigheid van de echo in het bepalen van het type schisis. De prenatale diagnoses van het type schisis kwamen in 76.9% (103/134) gevallen overeen met de postnatale bevindingen. Onderschatting van de ernst van de schisis gebeurde in 19.4% (26/134) en in 3.7% (5/134) gevallen werd de schisis ernstiger ingeschat dan deze postnataal bleek te zijn. Er werden geen fouten gemaakt in het onderscheid tussen unilaterale en bilaterale schisis. Deze resultaten suggereren dat de prenatale echo een redelijk betrouwbare techniek is voor het inschatten van de ernst van de schisis. Het voorspellen van het type schisis is belangrijk bij de counseling van ouders die een kind met een schisis verwachten. Het schisisteam en de gynaecoloog moeten zich wel bewust zijn van het feit dat een schisis van het palatum vaker wordt gemist, met andere woorden de ernst van de schisis wordt vaker onderschat met de echo. Deze studie diende als basis voor de ontwikkeling van een nieuwe classificatie die is gepresenteerd in **hoofdstuk 2**.
Bij het informeren van ouders over de uitkomst en prognose van schisis, is niet alleen het type, maar ook het risico op bijkomende afwijkingen behalve de schisis van belang. Vooral de kans op een onderliggende chromosomale afwijking kan de prenatale counseling en –beleid beïnvloeden. In **hoofdstuk 7**, wordt een overzicht gegeven van bijkomende afwijkingen en chromosomale abnormaliteiten die zich samen kunnen voordoen met schisis. Gegevens uit de literatuur zijn aangevuld met data van de Nederlandse Vereniging van Schisis en Craniofaciale Afwijkingen (NVSCA). De pre- en postnatale studies lieten zien dat de prevalentie van bijkomende afwijkingen het laagste is in CL (0-20.0% en resp. 7.6-41.1%). Bij CLP werd een hogere frequentie bijkomende afwijkingen gezien, namelijk in de prenatale studies een prevalentie van 39.1%-66% en in de postnatale studies 21.1-61.2%. Ondanks het feit dat CP bijna nooit

prenataal werd gedetecteerd, lieten de postnatale studies zien dat deze groep het vaakst samengaat met bijkomende afwijkingen, namelijk in 22.2-78.3%. Chromosomale afwijkingen werden het meest gezien bij schisis plus. Bij een, met echo, veronderstelde geïsoleerde schisis, werden bij CLP in 3.9% en bij CL in 1.8% (enkel 22q11 deleties) en 1.6% in CP. Deze systematic review toonde aan dat prenatale counseling ten aanzien van de prognose en risico op chromosomale afwijkingen afhankelijk is van het type schisis dat gezien wordt op de echo. De meest belangrijke factor in het voorspellen van de aanwezigheid van een chromosomale abnormaliteit is het voorkomen van bijkomende afwijkingen in combinatie met de schisis. Onafhankelijk van het type schisis, adviseren wij dan ook prenatale karyotypering in het geval van andere bijkomende afwijkingen bij schisis. Als er geen verdenking is op bijkomende afwijkingen, wordt karyotypering bij CL afgeraden, maar array- CGH zou overwogen kunnen worden. In veronderstelde geïsoleerde CLP of CP, werden prenataal invasieve testen, bij voorkeur met array-CGH geadviseerd.

Deel III Prenatale Counseling

In dit deel van het onderzoek gaan we op zoek naar factoren die mogelijk invloed hebben op de meningsvorming van ouders die een kind met een schisis verwachten. In de literatuur wordt gesuggereerd dat de houding van de professional van invloed kan zijn op het besluit van de ouders, met name ten aanzien van zwangerschapsafbreking. In **hoofdstuk 8** wordt de mening van de gynaecoloog over zwangerschapsafbreking bij geïsoleerde schisis vergeleken tussen Israël en Nederland. Deze twee landen zijn gekozen voor vergelijking, omdat het aantal ouders dat voor een zwangerschapsafbreking kiest bij geïsoleerde schisis in Israël hoog is en in Nederland laag. Door middel van vragenlijsten is gekeken naar de mening van de gynaecoloog ten aanzien van: ingeschatte ernst van een schisis, de ingeschatte mate van invloed van schisis op het levensgeluk van de ouders en het kind en de ingeschatte mate van invloed op dagelijks functioneren.

Daarnaast onderzochten we de mening van de professionals ten aanzien van de keuze voor zwangerschapsafbreking vanwege een geïsoleerde schisis. Nederlandse gynaecologen zien, in tegenstelling tot hun Israëlische collega's, schisis vaker als een afwijking [rate differences (RD) 17.8%, 95% CI: 0.5-33.1%]. In Nederland vindt

10.6% van de respondenten dat geïsoleerde schisis een reden kan zijn voor de keuze voor zwangerschapsafbreking. In Israel is dat 11.1% [RD 0.6%, 95% CI: -12-10.9%]. Concluderend verschillen de gynaecologen van beide landen niet substantieel van mening ten aanzien van de ernst van een schisis en de aanvaardbaarheid van zwangerschapsafbreking bij geïsoleerde schisis. Deze studie geeft dus geen verklaring voor het grote verschil in ratio zwangerschapsafbreking bij geïsoleerde schisis in Israël en Nederland.

In **hoofdstuk 9** is de mening van aanstaande ouders onderzocht ten aanzien van de ingeschatte ernst, belasting van een schisis en hun houding tegenover de keuze voor zwangerschapsafbreking bij geïsoleerde schisis. Tussen augustus 2011 en augustus 2014, is een prospectieve vragenlijst studie verricht onder zwangeren en hun partner die de prenatale schisispoli bezochten. De meeste aanstaande ouders beschrijven schisis als een "cosmetische afwijking" (43.6%) of als "net wat anders dan normaal" (26.6%). De ouders die schisis als zodanig beschrijven, verwachten dat schisis op zichzelf niet van invloed is op hun eigen – of op het levensgeluk van hun kind. Professionals van het schisisteam lijken van invloed te zijn op de meningsvorming van ouders. Een minderheid van de ouders (6.4%, 5/85) overwoog zwangerschapsafbreking maar uiteindelijk koos geen van de ouders voor die optie. De ingeschatte ernst van schisis en de verwachte invloed op het levensgeluk van het kind zijn twee significante factoren (p=0.04) op overwegen van een zwangerschapsafbreking. Deze studie suggereert dat de prenatale poli van het schisisteam waardevol is. Hoewel de leden van het schisisteam en de gynaecoloog moeten beseffen dat ze wel degelijk invloed hebben op de mening van ouders ten aanzien van de schisis.

Hoofdstuk 8 en 9 laten dus zien dat de aanstaande ouders en gynaecologen van mening verschillen ten aanzien van de ernst van een schisis. Tevens suggereren de studies dat de mening van de professional van invloed is op de aanstaande ouders. Dit tezamen benadrukt de invloed van prenatale counseling, zeker als de aanstaande ouders een zwangerschapsafbreking overwegen. Hoe bepalen we welke mate van een directieve houding een counselor mag aannemen?

In **hoofdstuk 10** worden drie types van counseling uitgelegd, te weten informatieve-, shared decision-making en paternalistische counseling. Door het bediscussiëren van pro- en contra argumenten voor al deze typen counseling kan de arts inzicht krijgen

in de ethische achtergrond van counseling en zich zo een mening vormen over dit praktische dilemma.

Concluderend geeft dit onderzoek inzicht in een nieuwe dimensie van schisiszorg, namelijk de prenatale fase. Bij de prenatale counseling van schisis komen meerdere aspecten aan bod; het postnatale plan, te weten de voeding, de chirurgische en ondersteunende behandeling, de cosmetische en functionele uitkomst, risico op gehoor- en spraakproblemen. Deze factoren hangen allen samen met het type schisis. Daarom is accurate diagnostiek en prenatale classificatie van uitermate groot belang. Daarnaast willen ouders geïnformeerd worden over het risico op bijkomende afwijkingen. Deze informatie tezamen bepaalt hun verwachte ernst en belasting van de schisis en hun houding ten aanzien van een mogelijk zwangerschapsafbreking. Dit onderzoek helpt niet alleen in het verbeteren van de te geven informatie, maar ook bij het bepalen van de toonzetting van counseling bij prenatale schisis.

Addendum

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List of Abbreviations

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LIST OF ABBREVATIONS

array CGH	array Comparative Genomic Hybridisation
BCD	Blepharo-Cheilo-Dontic (syndrome)
CI	Confidence Intervals
CL	Cleft Lip only
CLA	Cleft lip and Alveolus
CL ± P	Cleft Lip with or without Cleft Palate
CP	Cleft Palate only
EUROCAT	European Registry of Congenital Anomalies and Twins
FISH	Fluorescence In Situ Hybridisation
HWS	Health, Welfare, and Sport
IUFD	Intra-Uterine Fetal Death
ICD	International Classification of Diseases
IUCR	Intra-Uterine Growth Retardation
IQR	Interquartile Range
MC	Median Cleft
MCA	Multiple Congenital Anomalies
MLPA	Multiplex Ligation-dependent Probe Amplification
NVOG	Dutch Society for Gynaecology and Obstetrics
NVSCA	Dutch Society for Cleft Lip and Craniofacial Abnormalities
OC/OFC	Oral Cleft/Orofacial Cleft
PRS	Pierre Robin Sequence
PSA	Population Screening Act
RD	Rate Difference
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
SD	Standard Deviation
SNP array	Single Nucleotide Polymorphism array
TOP	Termination of Pregnancy
US	Ultrasound
VCF	Velo-Cardio-Facial syndrome (22q11.2 deletion)
VSD	Ventricular Septal Defect
2D	Two-dimensional
3D	Three-dimensional

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ACKNOWLEDGMENTS/DANKWOORD

Ooit op de dansvloer gestaan met plastisch chirurgen, kaakchirurgen, psychologen, orthodontisten, kno-artsen, klinisch genetici en tandartsen? Ik wel, in Götenburg, een mooiere afsluiting van zes jaar onderzoek in het Wilhelmina Kinderziekenhuis had ik me niet kunnen wensen. Het was een inspirerende periode. Soms moeilijk, er zitten helaas maar zeven dagen in de week, waarvan er sowieso vijf naar de opleiding gingen. Wetenschap bedrijven is een mooie uitdaging en bovenal een absolute toevoeging op de kliniek.

Het proefschrift is nu klaar en dat heb ik uiteraard niet alleen gedaan. Iedereen die aan het onderzoek heeft bijgedragen wil ik bedanken!

Prof. dr. M. Kon, promotor, beste professor. Vanaf het begin was u betrokken bij mijn onderzoek. Uw adviezen, luisterend oor en persoonlijke betrokkenheid waren zeer waardevol. Het was dankzij uw hulp dat de contacten in Israël tot stand kwamen. Onze bezoeken aan Haifa, Tel Aviv en Jeruzalem, eerst met z'n tweeën en later ook met Aebele en Henriette waren bijzonder. Uw enthousiasme voor het uitzoeken van de leukste restaurants en het organiseren van het culturele en historische aspect van de reizen zal ik nooit vergeten. Veel dank voor de fijne samenwerking!

Prof. dr. J.J.M. van Delden, promotor, beste Hans. Voor het ethische deel van dit proefschrift werd jouw hulp ingeroepen. En dat bleek onmisbaar. De conversaties in jouw kamer waren voor mij een letterlijke "vlucht" uit de chirurgische wereld en zette me weer met beide benen op de grond. Je liet mijn hersenen voor het eerst in de opleiding echt kraken en de literatuur die je me voorschotelde kon ik niet, zoals normaal doorheen racen, maar moest ik soms wel voor drie keer lezen voordat ik het begreep. Heel veel dank voor je vertrouwen, fijne gesprekken en veilige landing! Hartelijk!

Dr. A.B. Mink van der Molen, co-promotor, beste Aebele. De eerste keer dat wij elkaar ontmoeten had je meteen al honderd ideeën en plannen voor me. Dat is nooit

opgehouden. Ik bewonder jouw passie en oneindige enthousiasme voor je vak en de wetenschap. Je hebt een groot hart voor je opleidingsassistenten en je zal altijd achter ons staan. Ik heb me zeer gewaardeerd gevoeld bij jou en ik ben blij dat ik je collega ben geworden in het UMC Utrecht. Jij hebt me ongelooflijk gestimuleerd, heel veel dank!

Leden van de beoordelingscommissie, Prof.dr. V.V.A.M. Knoers, Prof.dr. R. Koole, Prof. dr. G.H.A. Visser, Prof.dr. C.M.A.M. van der Horst, Prof.dr. J. Gussekloo, dank voor het lezen en beoordelen van mijn proefschrift en uw deelname in de oppositie.

Dr. Swanenburg-de Veye, beste Henriette. Zonder jou was dit proefschrift er niet geweest. Jouw input en de inclusie van ouders voor ons onderzoek waren onmisbaar. Jouw jarenlange ervaring als psycholoog van het schisisteam, maar bovenal ook als wetenschapper waren zeer belangrijk. En wat was het fijn om af en toe stoom uit te blazen bij jou! Ik hoop dat we vaak nog even koffie drinken en wie weet in de toekomst wel als familie ;)

Dr. C.W.B. Boonacker, beste Chantal. Wat bewonder ik jou! Jouw nauwkeurigheid in het verwerken van de data en je hulp bij de statistiek waren zeer belangrijk. Maar bovenal je humor en passie voor je werk. Het was altijd heel gezellig! En wat ben ik blij, dat je ondanks persoonlijke problemen bij ons onderzoek betrokken bent gebleven. Heel veel dank!

Dr. M.J. van den Boogaard, beste Marie-José. Wat hebben we geploeterd met de cijfers! Maar dankzij jouw streven naar perfectie hebben we een prachtig artikel geschreven. Ook veel dank voor jouw input op het laatste moment.

Dr. L.R. Pistorius en dr. G.T.R Manten, gynaecologen, beste Lou en Wendy. Lou, je hebt me veel geholpen met de prenatale data, veel dank. Wendy, toen Lou naar Zuid-Afrika terug ging, heb jij het overgenomen. Veel dank voor je hulp met de echo gegevens en het kritisch lezen van mijn artikelen.

Dr. C.C. Breugem, beste Corstiaan. Initiator van de prenatale poli. Mede dankzij jou is het onderzoek geslaagd. Dank ook voor het kritisch lezen van mijn artikelen en input bij de embryologiestukken.

Charlotte Loozen, dank voor je bijdrage die je hebt geleverd aan dit proefschrift. Het was leuk om je wetenschappelijk te begeleiden. Heel veel succes met je promotieonderzoek bij de chirurgie.

Stafleden plastische chirurgie UMCU, eerst als assistent, nu als collega. Arnold, opleider, efficiënt opereren leer(de) ik van jou! Pascal, wat fijn om nog steeds met jou te opereren, bevlogen, geduldig, een fantastische microchirurg en hart voor je patiënten! Yvette, jij inspireerde mijn passie voor de mammachirurgie en ik heb grote bewondering voor het werk wat jij het afgelopen half jaar hebt verzet. Petje af! En dan tot slot Anne-Floor, nog even kamergenoten geweest! Het was heeel gezellig en ik hoop op nog veel etentjes, trekker rijden en champagne in Kerk-Avezaath!

Stafleden plastische chirurgie van het Antonius Ziekenhuis. Wat een superjaar heb ik gehad bij jullie, aan operaties geen gebrek!

Stafleden en arts-assistenten chirurgie van het Diakonessenhuis in Utrecht. Het is alweer even geleden, maar de basis van de heelkunde werd gelegd bij jullie. Heel veel dank daarvoor.

Beste arts-assistenten plastische chirurgie, eerst Paul, Dalibor, Miriam en Sven, jullie maakte de start in het UMCU zeer gezellig en leerzaam. Eline, heel wat tripjes waren samen met jou, je bent een fantastische chirurg en bevlogen collega! Later, Eva, Willemijn, Gilean, Margriet, Emma, Mireille, Roos, Robbert-Jan, Mischka en Alwine, dank voor de gezelligheid, biertjes en mooie ski-trips!

Bea en Margreet en later Janneke, secretaresses van de afdeling plastisch chirurgie, dank voor de thee/koffie en koekjes, ondersteunende woorden en luisterend oor! Onmisbaar voor onze afdeling!

Lieve, lieve, lieve jaarclub. Al meer dan tien jaar bij elkaar en nog altijd even hecht. Wat hebben we veel gedeeld met elkaar; liefde(sverdriet), reizen, borrels, foto's, bruiloften en andere feesten. Nu zelfs met mannen. Annelieke, mijn sportbuddy, onmisbaar in de drukte van de dag! Lieve Eef, wat een fijne gesprekken hebben wij! Zonder jullie was Utrecht een stuk minder leuk!

Laura en Hilde, vriendinnen van de studie, wat is het fijn om af en toe bij te kletsen en elkaar luisterend oor te zijn in de perikelen van de opleiding, onderzoek, en het medisch specialisten bestaan. Veel dank!

Lieve Linda, Fleur en Eva, al meer dan dertig jaar (en twintig jaar..) vriendinnen. Dat is toch heel bijzonder! Ondanks de afstand en baby's blijven we elkaar zien en dat nog hopelijk tot we bejaard zijn!

Lieve Hanneke Toemen, dank voor het terug vinden van de balans. Je hebt me overeind geholpen toen ik even wankelde, dat vergeet ik niet!

Mijn paranimfen; Michelle Ebbeling en Anna Janssen-Bakker;

Lieve Michelle, lief vriendinnetje! Samen de geneeskunde nerds van de jaarclub, maar ondertussen zoveel meer! Onze reis naar Afrika lijkt al zolang geleden, het was fantastisch mooi! Je bent er altijd voor me en dat lijkt normaal, maar is echt heel bijzonder. Ik bewonder jou als mens maar zeker ook als collega met hart voor je patiënten(tjes) en "oog voor detail". Jij weet als geen ander wie ik ben! Een vriendschap van goud!

Lieve Anna, weet je nog dat ik voor het eerst bij je kwam logeren? Het is al dertien jaar geleden, maar ik wist meteen dat je een van de warmste mensen bent die ik zou leren kennen! Jouw enthousiasme als vriendin is heel mooi en fijn. Jij bent altijd oprecht geïnteresseerd en ik ben heel blij dat je straks naast me staat, al is het ditmaal zonder toga ;)

Lieve familie van den Dungen, al die neven en nichten met fantastische carrières over heel de wereld, jullie zijn allemaal toppers! Lieve ooms en tantes, altijd interesse, en als ik wil overal een logeerplek, zo fijn! Familie Maarse, eindelijk nog een Maarse de promoveert! Yoehoe! Altijd hartelijk en gezellig bij jullie, dank!

Lieve Roeland sr. en Pauline, vanaf het eerste moment de fijnste schoonouders! Roeland sr., wat was het fijn om, zeker in de beginjaren, even mijn ervaringen als dokter met jou te delen. Jouw jarenlange ervaring als huisarts zette dingen in perspectief. Pauline, je bent een ontzettend warm persoon, dank voor je belangstelling in mijn onderzoek, werk en ik hoop op nog heel veel tripjes samen!

Lieve zusjes en broers de Wilde Marlieke, Sofieke, Maarten wat een promotienerds met z'n allen! Merijn, sorry voor alle medische gesprekken, eindelijk een niet-dokter in de familie, het werd tijd. Dank voor alle interesse!

Lieve Anouk, wat een fantastische schoonzus heb ik toch! Slim, doortastend en bovendien mijn persoonlijke bron in Den Haag! Altijd in voor een borrel! Dank voor alle interesse in mijn onderzoek.

Lieve Jan en Floor, broertje en zusje. Zo fijn dat ik jullie blonde grote zus mag zijn. Jan, wandelende encyclopedie, lolbroek, de band die wij hebben is heel belangrijk voor mij! In Utrecht waren we een act op de dansvloer en nu een reismaatje en nog steeds maak je me hard aan het lachen! Ik ben trots op je keuzes en je passie voor je werk. Lief zusje! We bellen dagelijks en bespreken zowat alles! Je bent een slimmerd en ik ben zo trots op jou! Ik hoop nu iets meer tijd te hebben om naar Amsterdam te komen, zodat we nog meer kunnen kletsen of opereren (?)!

Lieve pappa en mamma, de ambitie heb ik van jullie. 'De weide wereld in' is met de paplepel ingegoten! Het begon met eindeloos overhoren, wat een geduld, pappa de alfa en mamma de bèta, taart voor mijn enige onvoldoende ooit, en later de stimulatie om maar vooral zover mogelijk van Nijmegen weg te gaan studeren en voor alles te knokken! Pap je hebt zelfs nog mijn proefschrift 'nagekeken'. Dank voor alles!

Allerliefste Roeland, maatje en grote liefde. De allerbelangrijkste! Jij was er vanaf dag één bij! Zonder jou was dit proefschrift er zeker niet! Jouw talenknobbel, streef naar perfectie en niet te-stoppen-werklust hebben me zoveel geholpen. Twee jaar van elkaar gescheiden door onze gezamenlijke ambities, jij in Hopkins, ik hier, we zijn er alleen maar sterker door geworden. En nu twee boekjes binnen één maand. De moeilijke momenten van onderzoek doen, maar ook de leukste momenten, ik ben zo gelukkig dat ik ze met jou mocht delen. Met jou durf ik iedere uitdaging aan! Vanaf nu wat meer niet-medische dan ☺! Ik hou van je.