Int. J. Oral Maxillofac. Surg. 2019; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2020.05.005, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Research Paper
Cleft Lip and Palate

Undetected anomalies in foetuses with a prenatal diagnosis of isolated cleft

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Abstract. The aim of this study was to determine the rate of undetected additional anomalies following a prenatal diagnosis of isolated oral cleft. Data of all infants with a prenatal diagnosis of isolated oral cleft born between 2000 and 2015 were studied retrospectively. Additional anomalies detected after birth were categorized as minor or major and included structural and chromosomal anomalies. Isolated clefts of the lip (CL), lip and alveolus (CLA) and lip, alveolus, and palate (CLAP) were diagnosed prenatally in 176 live-born infants. The type of cleft was more extensive after birth in 34/176 (19.3%) and less extensive in 16/176 (9.1%) newborns. Additional anomalies were diagnosed in 24 infants (13.6%), of which 12 (6.8%) were categorized as major. The latter included two submicroscopic chromosome anomalies and two gene mutations. Postnatal additional anomalies occurred more frequently in CLA and CLAP than in CL, and more in bilateral than in unilateral clefts. Major anomalies are still found in infants with a prenatal diagnosis of an isolated oral cleft. The prevalence of additional anomalies seems to be related to the type and bilaterality of the cleft, and this should be considered during prenatal counselling.

Key words: genetic testing; prenatal diagnosis; cleft lip; cleft palate; prenatal ultrasonography.

Accepted for publication 11 May 2020

Oral cleft (OC) is the most common congenital craniofacial anomaly, with an incidence of 1:700[1]. The following phenotypes are distinguished: cleft lip (CL), cleft lip and alveolus (CLA), cleft lip, alveolus, and palate (CLAP), and cleft palate (CP)[1]. The likelihood of the presence of other structural anomalies and chromosomal anomalies increases when an oral cleft is diagnosed[2,3]. The presence of additional anomalies may result in a challenging start to life and may have a substantial impact on the (psychosocial) health of the child and parent[4,5]. Prenatal assessment is important to determine the type of OC and the presence of other anomalies in order predict the outcome. Counselling may enable parents to process disappointment and prepare for adjusted care during the pregnancy and after birth, rather than being confronted with difficulties when a child is born[6–10].

The introduction of the routine prenatal anomaly scan in the Netherlands in 2007 has increased the prenatal detection rate of CL, CLA, and CLAP substantially, from 5% in the 1980s to over 86% in the past decade[11,12]. Prenatal detection rates of isolated CP are low and remain challenging. This could be explained by the absence of obvious facial clues suggesting the presence of a CP when no other anomalies are suspected[13].

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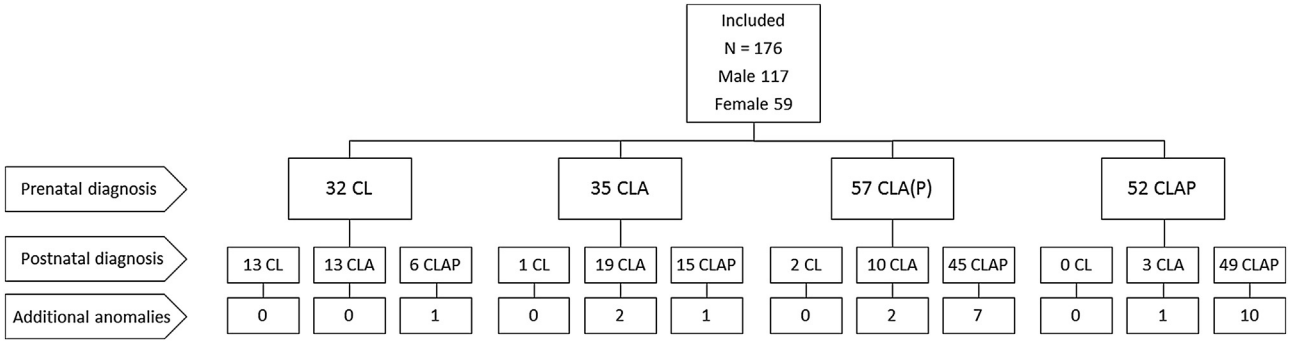

Fig. 1. Overview of results: prenatal apparent isolated oral clefts and postnatal additional anomalies.
Cleft type: CL, cleft lip; CLA, cleft lip and alveolus; CLAP, cleft lip, alveolus, and palate; CLA(P), cleft lip, alveolus, and (probably) palate.

Invasive prenatal testing is offered when an OC is diagnosed[11]. In our laboratory, foetal karyotyping was replaced by microarray analysis starting in 2011[14,15]. Despite advanced prenatal diagnostic methods, not all additional anomalies may or can be detected before birth. In 17 postnatal studies including 28,953 infants with OC, the prevalence of additional anomalies varied between 17% and 60%[16]. The rate of additional anomalies following a prenatally diagnosed isolated OC has been reported in only three studies in the recent literature (including 344 foetuses), with this rate varying between 10% and 30%[17–19]. These studies did not include data on chromosomal anomalies detected by means of microarray analysis.

The aim of this study was to evaluate the rate and severity of postnatally detected additional chromosomal aberrations and/or structural anomalies in infants with a prenatal diagnosis of isolated oral cleft in the South-West region of the Netherlands. The ultimate aim was to enable comprehensive prenatal counselling.

Materials and methods

This was a retrospective cohort study of all consecutive pregnancies with foetuses diagnosed with an isolated OC, live-born between January 2000 and May 2015 in the South-West region of the Netherlands. When an OC was suspected during the pregnancy, the prospective mother was referred to Erasmus MC, a tertiary referral hospital, for a prenatal expert ultrasound examination, including two-dimensional and three-dimensional ultrasound. When

Table 1. Prenatal diagnosis and postnatal outcome of 12 cases with prenatal apparent isolated cleft and minor postnatal additional anomalies.

Sex	Birth year	Prenatal diagnosis	Postnatal diagnosis	Side cleft	Prenatal genetic investigation	Postnatal structural anomalies	Postnatal syndromic anomalies	Postnatal genetic investigation	Death
F	2014	CLAP	CLAP	L	x	Pre-auricular fistula	None	x	No
M	2014	CLAP	CLAP	B	Normal microarray	ASD type II, mild peripheral pulmonary stenosis, syndactyly	None	x	No
M	2012	CLAP	CLA	B	Normal microarray	None	Van der Woude	IRF6 gene mutation (target mutation analysis)	No
F	2012	CLA	CLA	L	x	Cleft earlobe	None	x	No
F	2011	CLA(P)	CLAP	L	x	None	Van der Woude	x	No
M	2010	CLAP	CLAP	B	Normal karyotype	Perimembranous VSD, ASD type II	None	No CHD7 gene mutation (target mutation analysis), normal microarray	No
M	2010	CLA(P)	CLAP	L	x	Accessory auricle	None	x	No
F	2010	CLAP	CLAP	R	Normal karyotype	Syndactyly	None	x	No
M	2009	CLA(P)	CLAP	B	Normal karyotype	None	Amniotic band constriction left hand	x	No
M	2008	CLAP	CLAP	L	x	None	Van der Woude	x	No
M	2003	CLA	CLA	L	x	Syndactyly	None	x	No
F	2002	CLA(P)	CLAP	B	x	Congenital ectropion	BCD	CDH1 gene mutation (target mutation analysis)	No

ASD, atrial septal defect; B, bilateral; BCD, blepharocheilodontic syndrome; CLA, cleft lip and alveolus; CLAP, cleft lip, alveolus, and palate; CLA(P), cleft lip, alveolus, and (probably) palate; F, female; L, left; M, male; R, right; VSD, ventricular septal defect; 'x', not performed/not available.

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Table 2. Prenatal diagnosis and postnatal outcome of 12 cases with prenatal apparent isolated cleft and major postnatal additional anomalies.

Sex	Birth year	Prenatal diagnosis	Postnatal diagnosis	Side cleft	Prenatal genetic investigation	Postnatal structural anomalies	Postnatal syndromic anomalies	Postnatal genetic investigation	Death
M	2015	CLAP	CLAP	L	x	Subglottic stenosis	None	x	No
M	2014	CLAP	CLAP	L	Normal microarray	Microcephaly, hepatosplenomegaly, syndactyly, developmental delay	None	x	No
M	2014	CLAP	CLAP	L	x	Choanal atresia, chorioretinal coloboma, VSD, laryngomalacia, malformation falx cerebri, deafness, Ebstein anomaly	CHARGE	CHD7 gene mutation (c.1828dupG) (target mutation analysis)	Yes, at 4.5 months (infectious respiratory failure)
F	2013	CL	CLAP	L	x	Radioulnar synostosis	None	x	No
F	2012	CLA	CLAP	R	x	Anterior ectopic anus, peripheral pulmonary stenosis, developmental delay	None	arr[hg18] 3p21.31p14.1 (48,012,380-64,294,973)x3 16.3 Mb 3p21 duplication	No
F	2012	CLAP	CLAP	L	x	Unilateral microtia/unilateral external auditory canal atresia, accessory auricle	None	x	No
F	2010	CLA(P)	CLAP	L	Normal karyotype	Patent ductus arteriosus, ASD type II, severe pulmonary stenosis, epilepsy, psychomotor retardation	Wolf–Hirschhorn	arr[hg18] 4p16 (38,283-8,321,040) x1 8.3 Mb 4p deletion	Yes, at 31 months (infectious respiratory failure)
M	2009	CLA(P)	CLAP	R	x	Developmental delay	None	arr[hg19] 6p21.1 (41318438-44676420)x1 3.4 Mb 6p21.1 deletion	No
M	2008	CLA(P)	CLA	B	x	Ectopic posterior pituitary glands, persisting cavum septi pellucidi, ASD type II (clinically insignificant), mild glandular hypospadias, psychomotor retardation, congenital dysplasia of the hip	None	Derivative chromosome 3 der(3)del(3)(p25.3) inv dup(3) (p22.3p25.3) arr[hg18] 3p26.3p 25.3(48,603-8,994,748) x1,3p25.3p22.3 (9021906-36061113)x3 8.9 Mb 3p deletion 27 Mb 3p duplication	No
F	2008	CLAP	CLAP	B	x	Congenital nasal cyst with extension into the intracranial space, congenital filamentous adhesion of the upper and lower eyelids	BCD	CTNND1 gene mutation (target mutation analysis)	No
M	2004	CLA(P)	CLA	R	Normal karyotype	Craniofacial microsomia, microtia, external auditory canal atresia, scoliosis	Goldenhar	x	No
M	2002	CLA(P)	CLAP	B	Normal karyotype	Oesophageal atresia, hypertrophic pyloric stenosis	None	x	No

ASD, atrial septal defect; B, bilateral; BCD, blepharocheilodontic syndrome; CHARGE, coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities; CL, cleft lip; CLA, cleft lip and alveolus; CLAP, cleft lip, alveolus, and palate; CLA(P), cleft lip, alveolus, and (probably) palate; F, female; L, left; M, male; R, right; VSD, ventricular septal defect; 'x', not performed/not available.

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the OC was confirmed, invasive genetic prenatal testing was offered to identify any chromosomal aberrations. From 2000 to 2011, conventional karyotyping was available as a routine diagnostic tool. In mid-2011, microarray genomic testing was introduced as common practice. Prospective parents were counselled by the 'cleft team' on the prognosis and treatment options prior to 24 weeks of gestation[20]. Psychosocial support was available. Following birth, the infant was examined by a paediatric specialist. The type of cleft (CL/CLA/CLAP/CP) was confirmed or revised. The extent of the oral cleft (unilateral/bilateral) was determined. If dysmorphic features or an abnormal development were suspected, the child was also examined by a clinical geneticist and if indicated, a targeted mutation analysis was performed.

Data were extracted from the hospital's electronic health records (Elpado/Astraia). Based on the ultrasound reports, the type of cleft was categorized as CL, CLA, CLA (P), or CLAP. The CLA(P) type was assigned when following the diagnosis of CLA, the presence of a cleft palate was noted as 'probable but could not be ascertained on the sonographic images obtained'. Isolated cleft palates were not detected prenatally and hence where not included in this study. The postnatal data were reviewed by a clinical geneticist, who categorized any additional anomalies into minor or major. This was based on the clinical relevance; abnormalities resulting in any permanent functional impairment were considered major. The cases with chromosomal aberrations were re-evaluated by a laboratory specialist. Terminated pregnancies ($n = 5$) and premature deliveries ($n = 1$) were excluded because phenotypic data were lacking.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 21.0 software (IBM Corp., Armonk, NY, USA). Associations between the prenatal and postnatal type of OC and postnatal additional anomalies were tested by logistic regression analysis. Probabilities less than 0.05 were regarded as being significant.

Results

The data of 176 live-born infants diagnosed prenatally with an isolated OC were included. The postnatal follow-up period ranged from 1.4 to 16.2 years (median 6 years).

Prenatal data

During prenatal expert ultrasound examination, 32 (18.2%) foetuses were diagnosed with CL, 35 (19.9%) with CLA, 52 (29.5%) with CLAP, and 57 (32.4%) with CLA(P) (Fig. 1).

Postnatal data

Postnatal clinical assessment of the OC confirmed the ultrasound diagnosis in 126/176 (71.6%) infants, while 50 (28.4%) diagnoses were revised (Fig. 1): 34 (19.3%) to a more extensive type and 16 (9.1%) to a less extensive type of cleft. A submucous cleft of the palate was determined in two infants with a prenatal diagnosis of CL and in two with CLA. (Bi) laterality was revised in 13/176 (7.4%) infants; seven prenatally unilateral clefts were diagnosed as bilateral and six prenatally bilateral clefts were diagnosed as unilateral after birth. A unilateral cleft was seen in 143 (81.3%) infants (15 CL, 39 CLA, 89 CLAP) and a bilateral cleft in 33 (18.8%) infants (1 CL, 6 CLA, 26 CLAP). Ninety-seven of the unilateral clefts (67.8%) were left-sided and 46 (32.2%) were right-sided.

Postnatal assessment of associated structural and syndromic anomalies

Additional anomalies were found in 24/176 (13.6%) infants with a prenatally apparent isolated oral cleft; 12 (6.8%) were categorized as minor (0 CL, 3 CLA, 9 CLAP) and 12 (6.8%) were categorized as major (0 CL, 2 CLA, 10 CLAP) (Tables 1 and 2). A higher prevalence of additional anomalies was noted with increasing severity of the type of cleft in reference to cleft lip only (CLA: odds ratio (OR) 2.91, 95% confidence interval (CI) 0.29–29.45; CLA(P): OR 5.81, 95% CI 0.70–48.2; CLAP: OR 8.32, 95% CI 1.02–67.9). Additional anomalies were diagnosed in 16/143 (11.2%) infants with a unilateral oral cleft and in 8/33 (24.2%) infants with a bilateral oral cleft (OR 2.54, 95% CI 0.98–6.57). No statistical significance was found.

All infants with additional anomalies categorized as major had multiple anomalies. Eleven of the 12 infants with anomalies categorized as minor had a single anomaly. Fig. 2 shows the distribution of the additional structural anomalies by organ system. Chromosomal aberrations and gene mutations associated with known syndromes were diagnosed in 8/176 (4.5%) infants (one Van der Woude syndrome, two blepharocheilodontic syndrome (BCD), one CHARGE syndrome, and four pathogenic chromosomal aberrations, of which one was associated with Wolf–Hirschhorn syndrome). Syndromic disorders were clinically diagnosed in 3/176 (1.7%) cases (two Van der Woude and one Goldenhar syndrome). Two patients died due to respiratory failure as a result of a viral pulmonary infection, one at 4.5 months after birth and the other at 31 months. Both had been diagnosed with a syndromic disorder (CHARGE syndrome and Wolf–Hirschhorn syndrome).

Chromosomal aberrations and prenatal cytogenetic diagnosis

Invasive prenatal testing was performed in 87/176 (49.4%) pregnancies; 54/176 (30.7%) by karyotyping and 33/176 (18.7%) by microarray analysis. Eight of the 87 infants who had undergone amniocentesis (9.2%) were diagnosed with additional anomalies during the postnatal period, of which four were major. One infant with a prenatal normal karyotype was diagnosed postnatally with a submicroscopic 4p deletion associated with

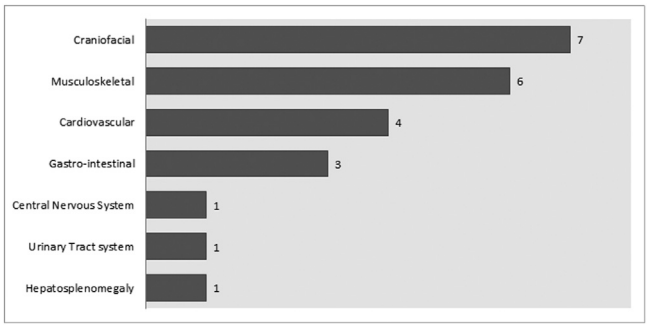

Fig. 2. Distribution of additional structural anomalies by organ system.

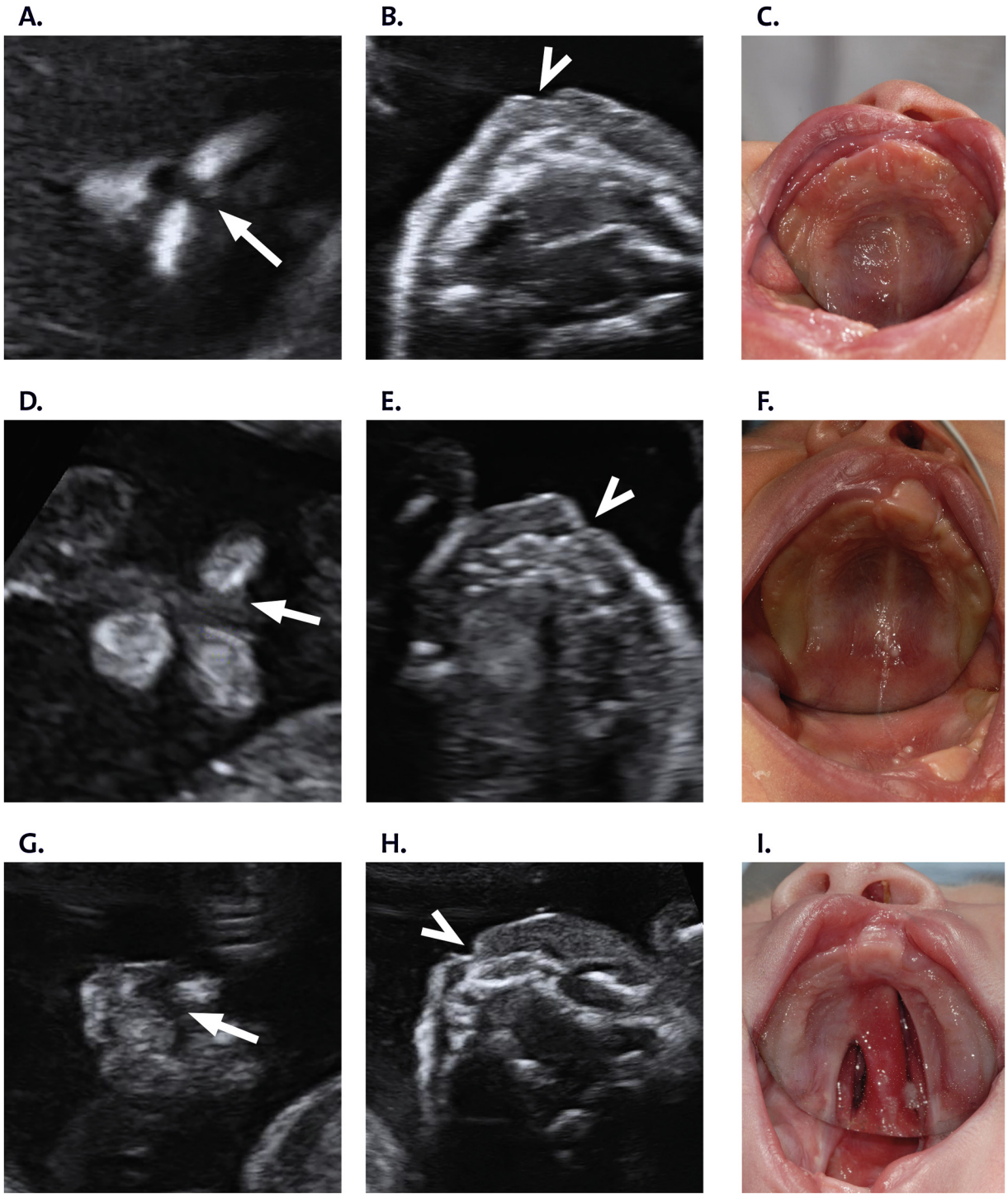

Fig. 3. Three examples of the prenatal and postnatal diagnosis. (A–C) Prenatal diagnosis of cleft lip (CL), confirmed after birth (CL). (D–F) Prenatal diagnosis of cleft lip (CL), revised to cleft lip and alveolus (CLA) after birth. (G–I) Prenatal diagnosis of cleft lip (CL), revised to cleft lip, alveolus, and palate (CLAP) after birth. Arrows indicate the cleft lip in the coronal ultrasound image. Arrowheads indicate the cleft lip and apparent intact alveolus and palate.

Wolf–Hirschhorn syndrome identified by microarray analysis. Prenatal microarray analysis was not routinely available at the time of pregnancy.

Amniocentesis was declined by 89 (50.6%) pregnant women. Postnatal genomic microarray revealed chromosomal aberrations in the offspring of three of these women (3.4%), which were categorized as major: two microscopically visible (3p21 duplication and a derivative chromosome 3) and one submicroscopic

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aberration associated with developmental delay and likely causal for CLAP (3.4 Mb 6p21.1 deletion)[21,22]. In two of these cases, additional structural anomalies were found, and developmental delay was detected in all three during follow-up. Furthermore, postnatal targeted mutation analysis identified two gene mutations in the major group (a CHD7 mutation associated with CHARGE syndrome and a CTNND1 mutation associated with BCD syndrome) and two gene mutations in the minor group (an IRF6 mutation associated with Van der Woude syndrome and a CDH1 mutation associated with BCD syndrome).

Discussion

Additional congenital structural anomalies and/or constitutive chromosomal aberrations were found in 13.6% of patients, half of which were considered as major. The prenatal diagnosis of the type of cleft was revised to a more extensive type in 34 (19.3%) infants and to a less extensive type in 16 (9.1%).

No false-positive prenatal cleft diagnoses were noticed, confirming earlier studies[18,23,24]. The prenatal diagnosis of the type of cleft was revised in 28.4% of infants, which compares well with the 30% and 35% found in previous studies[12,18]. The revisions were most common in the CL group. The prenatal diagnosis of CL was revised in 19/32 (59.4%) cases to a more extensive type (CLA or CLAP), and one infant with CLAP was also revealed to have a radioulnar synostosis. These revisions could be explained by the challenging detection of mild alveolar notches and (submucous) cleft palate, as reported previously by several authors and shown in Fig. 3[25–27]. No additional structural anomalies or chromosomal aberrations were found in infants with a postnatal diagnosis of CL.

The type and extent of the OC is related to the prevalence of additional anomalies[2,3,16,24]. The present study data confirm these findings, as the frequency of additional anomalies increased with involvement of the alveolus and the palate. Only this study and the study by Depla et al.[28] have reported the prenatal diagnoses of CL, CLA, and CLAP subdivisions, suggesting differences in the prevalence of additional anomalies.

Additional anomalies were diagnosed more frequently in infants with a bilateral cleft compared to a unilateral cleft, as also reported by Hagberg et al.[29] and Fleurke-Rozema et al.[12].

In the majority of cases, the prenatal diagnosis was determined prior to 24 weeks of gestation. The additional structural anomalies not detected until after birth were anomalies that may only become evident late in gestation (microcephaly and severe pulmonary stenosis)[30,31] or anomalies known to be difficult to diagnose due to the variable presentation of abnormal structures. Examples of the latter are Ebstein anomaly, ventricular septal defect, anterior ectopic anus, and oesophageal atresia[31–34]. Similar anomalies were not detected before birth in two recent studies, indicating the limitations of ultrasound in pregnancy[18,28].

Two of the four patients with an aberrant chromosome status carried a large chromosomal aberration (3p duplication and derivative chromosome 3); the other two carried submicroscopic aberrations (6p21 deletion and 4p deletion). Novel high-resolution genetic tests such as microarray-based genomic analysis can detect all of these chromosomal aberrations, in contrast to conventional karyotyping, which has a limited resolution[35]. The use of this technique reduces the rate of undetected chromosomal aberrations associated with structural and syndromic malformations[36]. Contrary to past opinions[15,37,38], we believe that invasive genetic testing for all types of OC is justified in view of the occasional inconsistencies in the pre- and postnatal diagnosis of the type of cleft in relation to the prevalence of additional anomalies, the introduction of microarray analysis, and the low additional risk of foetal loss following amniocentesis[12,37,38]. Microarray testing may reveal chromosomal aberrations associated with features that cannot be detected on ultrasound, such as developmental delay or hypotony, but which strongly influence the foetal prognosis. Although microarray testing is offered in all pregnancies with anomalies detected on ultrasound, parents often decline genetic testing, as revealed in the present study and a previous Dutch study[12]. Prior to the microarray era, the risk of an abnormal karyogram associated with OC was low[39]. This might have influenced counselling concerning invasive procedures. Cultural attitudes in the Netherlands, in addition to parental fear of miscarriage could also have played a role, despite the low risk of pregnancy loss[37,40].

In addition to the chromosomal aberrations detected postnatally by microarray analysis, gene mutations were identified using targeted mutation analysis, of which two were major anomalies (CHARGE and BCD with intracranial extension). If prenatal diagnosis using microarray and whole exome sequencing (WES) was performed in all cases, the diagnosis of additional genetic anomalies would have been possible before birth in an additional 4.5% (8/176).

The strengths of this study are the large sample size, the subdivision of cleft types (CL, CLA, CLAP) and extent (unilateral/bilateral), and the reporting on the additional value of microarray analysis. A main limitation is the retrospective nature. The shorter follow-up period of infants born in the last 2 years of the study might have resulted in an underestimation of the rate of associated anomalies (especially milder developmental delay, speech disorders, and intellectual disability revealed later in life). Moreover, submicroscopic aberrations and gene mutations were not tested and excluded in all of the cases during the follow-up period.

In conclusion, additional anomalies were seen in almost one in every 7.5 infants diagnosed prenatally with an isolated OC. The introduction of microarray analysis has increased the diagnosis of chromosomal aberrations. Involvement of the alveolus and the palate and a bilateral cleft appear to be related to a higher risk of additional anomalies. The diagnosis of only a CL during prenatal screening does not rule out the presence of associated anomalies postnatally, taking into account the revision rate of the type of cleft after birth. Possible inconsistencies with the final postnatal diagnosis of the type of cleft and the rate of undetected additional anomalies should be discussed during prenatal parental counselling.

Patient consent

Not required.

Funding

None.

Ethical approval

Data collection and protection took place according to the privacy regulations of the Erasmus MC. Approval was not required according to the judgement obtained from the Ethics Review Board of the Erasmus MC, Rotterdam, the Netherlands (MEC-2016-576).

Competing interests

The authors have no conflicts of interest to declare.

References

1. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet* 2009;**374**:1773–85.
2. Kraus BS, Kitamura H, Ooe T. Malformations associated with cleft lip and palate in human embryos and fetuses. *Am J Obstet Gynecol* 1963;**86**:321–8.
3. Milerad J, Larson O, Hagberg C, Ideberg M. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. *Pediatrics* 1997;**100**(2 Pt 1):180–6.
4. Klassen AF, Tsangaris E, Forrest CR, Wong KW, Pusic AL, Cano SJ, Syed I, Dua M, Kainth S, Johnson J, Goodacre T. Quality of life of children treated for cleft lip and/or palate: a systematic review. *J Plast Reconstr Aesthet Surg* 2012;**65**:547–57.
5. Sell D, Sweeney T, Harding-Bell A, John AK. Measuring quality of life in cleft lip and palate patients: currently available patient-reported outcomes measures. *Plast Reconstr Surg* 2012;**130**:888e.
6. Davalbhakta A, Hall PN. The impact of antenatal diagnosis on the effectiveness and timing of counselling for cleft lip and palate. *Br J Plast Surg* 2000;**53**:298–301.
7. Aspinall CL. Dealing with the prenatal diagnosis of clefting: a parent's perspective. *Cleft Palate Craniofac J* 2002;**39**:183–7.
8. Johansson B, Ringsberg KC. Parents' experiences of having a child with cleft lip and palate. *J Adv Nurs* 2004;**47**:165–73.
9. Rey-Bellet C, Hohlfeld J. Prenatal diagnosis of facial clefts: evaluation of a specialised counselling. *Swiss Med Wkly* 2004;**134**:640–4.
10. Nusbaum R, Grubs RE, Losee JE, Weidman C, Ford MD, Marazita ML. A qualitative description of receiving a diagnosis of clefting in the prenatal or postnatal period. *J Genet Couns* 2008;**17**:336–50.
11. Ensing S, Kleinrouweler CE, Maas SM, Bilardo CM, Van der Horst CM, Pajkrt E. Influence of the 20-week anomaly scan on prenatal diagnosis and management of fetal facial clefts. *Ultrasound Obstet Gynecol* 2014;**44**:154–9.
12. Fleurke-Rozema JH, van de Kamp K, Bakker MK, Pajkrt E, Bilardo CM, Snijders RJ. Prevalence, diagnosis and outcome of cleft lip with or without cleft palate in The Netherlands. *Ultrasound Obstet Gynecol* 2016;**48**:458–63.
13. Abramson ZR, Peacock ZS, Cohen HL, Choudhri AF. Radiology of cleft lip and palate: imaging for the prenatal period and throughout life. *Radiographics* 2015;**35**:2053–63.
14. Srebniak M, Boter M, Oudesluijs G, Joosten M, Govaerts L, Van Opstal D, Galjaard RJ. Application of SNP array for rapid prenatal diagnosis: implementation, genetic counselling and diagnostic flow. *Eur J Hum Genet* 2011;**19**:1230–7.
15. Srebniak MI, Boter M, Oudesluijs GO, Cohen-Overbeek T, Govaerts LC, Diderich KE, Oegema R, Knapen MF, van de Laar IM, Joosten M, Van Opstal D, Galjaard RJ. Genomic SNP array as a gold standard for prenatal diagnosis of foetal ultrasound abnormalities. *Mol Cytogenet* 2012;**5**:14.
16. Maarse W, Rozendaal AM, Pajkrt E, Vermeij-Keers C, Mink van der Molen AB, van den Boogaard MJ. A systematic review of associated structural and chromosomal defects in oral clefts: when is prenatal genetic analysis indicated? *J Med Genet* 2012;**49**:490–8.
17. Chmait R, Pretorius D, Moore T, Hull A, James G, Nelson T, Jones M. Prenatal detection of associated anomalies in fetuses diagnosed with cleft lip with or without cleft palate in utero. *Ultrasound Obstet Gynecol* 2006;**27**:173–6.
18. Burnell L, Verchere C, Pugash D, Loock C, Robertson S, Lehman A. Additional postnatal diagnoses following antenatal diagnosis of isolated cleft lip +/- palate. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**:F286–290.
19. Depla AL, Breugem CC, van der Horst CM, de Heus R, van den Boogaard MH, Maas SM, Pajkrt E, Bekker MN. Polyhydramnios in isolated oral cleft pregnancies: incidence and outcome in a retrospective study. *Prenat Diagn* 2017;**37**:162–7.
20. Exalto N, Cohen-Overbeek TE, van Adrichem LN, Oudesluijs GG, Hoogeboom AJ, Wildschut HI. Prenataal vastgestelde orofaciale schisis [Prenatally detected orofacial cleft]. *Ned Tijdschr Geneeskd* 2009;**153**. B316. Dutch.
21. Cobourne MT. The complex genetics of cleft lip and palate. *Eur J Orthod* 2004;**26**:7–16.
22. Hill C, Jacobs B, Kennedy L, Rohde S, Zhou B, Baldwin S, Goudy S. Cranial neural crest deletion of VEGFa causes cleft palate with aberrant vascular and bone development. *Cell Tissue Res* 2015;**361**:711–22.
23. Matthews MS, Cohen M, Viglione M, Brown AS. Prenatal counseling for cleft lip and palate. *Plast Reconstr Surg* 1998;**101**:1–5.
24. Bergé SJ, Plath H, Van de Vondel PT, Appel T, Niederhagen B, Von Lindern JJ, Reich RH, Hansmann M. Fetal cleft lip and palate: sonographic diagnosis, chromosomal abnormalities, associated anomalies and postnatal outcome in 70 fetuses. *Ultrasound Obstet Gynecol* 2001;**18**:422–31.
25. Maarse W, Bergé SJ, Pistorius L, van Barneveld T, Kon M, Breugem C, Mink van der Molen AB. Diagnostic accuracy of transabdominal ultrasound in detecting prenatal cleft lip and palate: a systematic review. *Ultrasound Obstet Gynecol* 2010;**35**:495–502.
26. Maarse W, Pistorius LR, Van Eeten WK, Breugem CC, Kon M, Van den Boogaard MJ, Mink van Der Molen AB. Prenatal ultrasound screening for orofacial clefts. *Ultrasound Obstet Gynecol* 2011;**38**:434–9.
27. Loozen CS, Maarse W, Manten GT, Pistorius L, Breugem CC. The accuracy of prenatal ultrasound in determining the type of orofacial cleft. *Prenat Diagn* 2015;**35**:652–5.
28. Depla AL, Breugem CC, van der Horst CM, de Heus R, van den Boogaard MH, Maas SM, Pajkrt E, Bekker MN. Polyhydramnios in isolated oral cleft pregnancies: incidence and outcome in a retrospective study. *Prenat Diagn* 2017;**37**:162–7.
29. Hagberg C, Larson O, Milerad J. Incidence of cleft lip and palate and risks of additional malformations. *Cleft Palate Craniofac J* 1998;**35**:40–5.
30. Leibovitz Z, Daniel-Spiegel E, Malinger G, Haratz K, Tamarkin M, Gindes L, Schreiber L, Ben-Sira L, Lev D, Shapiro I, Bakry H, Weizman B, Zreik A, Egenburg S, Arad A, Tepper R, Kidron D, Lerman-Sagie T. Prediction of microcephaly at birth using three reference ranges for fetal head circumference: can we improve prenatal diagnosis? *Ultrasound Obstet Gynecol* 2016;**47**:586–92.
31. van Velzen CL, Clur SA, Rijlaarsdam ME, Bax CJ, Pajkrt E, Heymans MW, Bekker MN, Hruda J, de Groot CJ, Blom NA, Haak MC. Prenatal detection of congenital heart disease—results of a national screening programme. *BJOG* 2016;**123**:400–7.
32. de Jong EM, de Haan MA, Gischler SJ, Hop W, Cohen-Overbeek TE, Bax NM, de Klein A, Tibboel D, Grijseels EW. Pre- and postnatal diagnosis and outcome of fetuses and neonates with esophageal atresia and tracheoesophageal fistula. *Prenat Diagn* 2010;**30**:274–9.
33. Dearani JA, Mora BN, Nelson TJ, Haile DT, O'Leary PW. Ebstein anomaly review: what's now, what's next? *Expert Rev Cardiovasc Ther* 2015;**13**:1101–9.
34. Lee MY, Won HS, Shim JY, Lee PR, Kim A, Lee BS, Kim EA, Cho HJ. Sonographic determination of type in a fetal imperforate anus. *J Ultrasound Med* 2016;**35**:1285–91.
35. de Wit MC, Srebniak MI, Govaerts LC, Van Opstal D, Galjaard RJ, Go AT. Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature. *Ultrasound Obstet Gynecol* 2014;**43**:139–46.
36. Srebniak MI, Van Opstal D, Joosten M, Diderich KE, de Vries FA, Riedijk S, Knapen MF, Go AT, Govaerts LC, Galjaard RJ. Whole-genome array as a first-line cytogenetic test in prenatal diagnosis. *Ultrasound Obstet Gynecol* 2015;**45**:363–72.

Please cite this article in press as: Haj M, et al. Undetected anomalies in foetuses with a prenatal diagnosis of isolated cleft, *Int J Oral Maxillofac Surg* (2020), https://doi.org/10.1016/j.ijom.2020.05.005

37. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015;**45**:16–26.
38. Wulff CB, Gerds TA, Rode L, Ekelund CK, Petersen OB, Tabor A. Danish Fetal Medicine Study Group. Risk of fetal loss associated with invasive testing following combined first-trimester screening for Down syndrome: a national cohort of 147,987 singleton pregnancies. *Ultrasound Obstet Gynecol* 2016;**47**:38–44.
39. Gillham JC, Anand S, Bullen PJ. Antenatal detection of cleft lip with or without cleft palate: incidence of associated chromosomal and structural anomalies. *Ultrasound Obstet Gynecol* 2009;**34**:410–5.
40. van den Heuvel A, Marteau TM. Cultural variation in values attached to informed choice in the context of prenatal diagnosis. *Semin Fetal Neonatal Med* 2008;**13**:99–102.

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Please cite this article in press as: Haj M, et al. Undetected anomalies in foetuses with a prenatal diagnosis of isolated cleft, *Int J Oral Maxillofac Surg* (2020), https://doi.org/10.1016/j.ijom.2020.05.005