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Prevalence, diagnosis and outcome of oral clefts in Singapore: An aid to counselling in an Asian population

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Abstract

Objectives: To assess the antenatal detection rate of oral clefts (isolated and complex) and pregnancy outcomes (karyotypic abnormalities and live-birth rates) in a tertiary referral center, to provide a basis for prenatal counselling and invasive diagnostics.

Methods: This was a retrospective review of cases with postnatal diagnosis of oral cleft from the KK Women's and Children's Hospital Maternal Fetal Medicine Department's Birth Defect database. Cases with estimated delivery dates between 1 January 2011 and 31 December 2015 were included. Demographic data, ultrasound soft markers, structural abnormalities, fetal karyotyping results and pregnancy outcomes were collected.

Results: Seventy- eight cases of oral cleft were confirmed postnatally. Local prevalence was 13.6 per 10,000 live births, with an overall detection rate of 93.1%. The male to female ratio was1.28:1. Detection rate for isolated oral clefts was significantly higher compared to complex oral clefts [100.0% vs 66.7% p=0.0003]. The proportion of parents opting for karyotyping in isolated and complex clefts was similar [60.0% vs 64.3%]. Abnormal karyotype was found in 4.2% of isolated CL ± P compared to 11.1% in fetuses with complex CL ± P (p=1).

Fetuses with median clefts were more likely to have associated congenital anomalies, with a poorer prognosis in terms of live-birth rates. While the live-birth rates for isolated or complex clefts was not significantly different [p=0.0695], neonates with isolated cleft had a higher survival rate [p<0.0001].

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Conclusions: The prevalence in our local population is lower than previously published. Our results validates a consistent finding that median clefts were more likely to be associated with congenital anomalies with poorer prognoses. The rate of abnormal karyotype (4.2% - 11.1%) found in oral clefts highlight the need to offer further diagnostic testing when detected. This body of evidence based on a heterogeneous Asian population would be of value in counselling parents with an antenatally diagnosed fetal cleft.

Introduction

Cleft lip with or without cleft palate (CL ± P) is a common facial congenital malformation, with incidence of 10-20 in 10,000 live births [1,2]. The incidence of CL ± P varies according to race and geographical regions. Recent European studies have consistently demonstrated an incidence of 16- 18 per 10,000 live births [3-5], with a higher incidence noted amongst Asian populations [5,6].

CL ± P may be found in isolation, or in association with other congenital malformations. It is a known phenotypic component of syndromes or chromosomal abnormalities [7,8]. Approximately more than 100 genetic syndromes and chromosomal abnormalities have been linked to facial clefting [9,10]. It is thus important for clinicians to provide relevant and accurate counselling when CL ± P is detected prenatally.

Despite a reported higher incidence amongst Asian populations, there has been a dearth of information with regard to the prevalence, detection rates, associated anomalies and outcomes from Asian tertiary referral centres, impeding clinical counselling based on local population data.

Objective

This study is a five-year retrospective review designed to assess the antenatal detection rate of CL ± P in a multi-racial Asian population, based on a large tertiary referral hospital's experience. Associated anomalies, and pregnancy outcomes in terms of karyotypic abnormalities and live-birth rates were also considered, so as to provide a basis for prenatal counselling and prenatal invasive diagnostics.

Methods

This was a retrospective review of cases diagnosed with CL ± P obtained from the KK Women's and Children's Hospital Maternal Fetal Medicine Department's Birth Defect Registry. Cases with EDD between 1 January 2011 and 31 December 2015 were included in this review.

Our department protocol offers dating scans between 8-10 weeks, first trimester screening for aneuploidies at 11-13 weeks and a routine anomaly scan at 18-23 weeks. All antenatally diagnosed CL ± P were offered invasive prenatal testing for fetal karyotyping. In affected cases, management strategies including termination of pregnancy (if the defect was detected before 24 weeks of gestation) were discussed. In ongoing pregnancies, targeted follow-up ultrasound examinations were performed. Each newborn was examined by a neonatologist prior to discharge from hospital.

Maternal and neonatal medical records were reviewed. Maternal and fetal characteristics, including demographic data, gestational age at diagnosis, ultrasound findings of other structural abnormalities, fetal karyotyping results and pregnancy outcomes were collected. A subdivision was made between isolated cases, i.e. those without other structural abnormalities, and those associated with other structural abnormalities.

For fetuses with an antenatal diagnosis of CL ± P, the ultrasound findings and any additional anomalies were correlated with the postnatal findings.

Statistical analysis

Statistical analysis was performed with SPSS version 22 for Windows. A *P*-value of <0.05 was considered to be statistically significant.

The chi-square test or Fisher's exact test was used to compare differences between groups.

Table 1: Characteristics of the study population

Characteristic				
	Isolated CL ± P (n=56)		**Additional anomalies (n=22)**	
Median Maternal age at EDD (years)	**30 (19 to 39)**		**33 (20 to 42)**	
Race				
Chinese	34 (60.71%)		16 (72.73%)	
Malay	11 (19.64%)		3 (13.64%)	
Indian	8 (14.29%)		2 (9.09%)	
Others	3 (5.36%)		1 (4.55%)	
Median gestation of diagnosis (weeks)	**20**		**22**	
Fetal sex				
Male	31		10	
Female	21		11	
Unrecorded	4		1	
Karyotype				
Not examined	25		7	
Normal	30		11	
Abnormal				
• Trisomy 13	0		2	
• Trisomy 18	0		2	
• Others	1		0	
Type of Cleft				
Unilateral*	39		13	
Right / Left	27	12	5	8
Bilateral	10		2	
Median	2		2	
Not specified	5		5	

Results

The baseline population characteristics were: Chinese (76.2%), Malays (15.0%) Indians (7.4%) and Others (1.4%) based on population data in 2012, a trend which has held consistent in the last decade from 2008 – 2018.

124 cases of CL ± P were identified based on examination of the department's birth defect registry. 78 cases of CL ± P were confirmed on postnatal examination. 22 cases were lost to follow up as they were not delivered in our hospital. The prevalence was stable during the study period, (18.1 per 10,000 live births in 2011, 14.6 in 2012, 12.0 in 2013, 10.4 in 2014 and 12.6 in 2015) and overall prevalence was 13.6 per 10,000 live births. The male to female ratio of CL ± P was 1.28

Gestation at diagnosis

The 20-week anomaly scan was offered as part of routine practice at our centre. There were no cases in which the anomaly scan was refused.

The majority of antenatally detected CL ± P were detected during the second trimester 84.4% (98/116), with 2 cases detected in the first trimester. 12.9% of clefts (15/116) were detected in the third trimester. 8 cases were found to have clefts postnatally, but these were not detected antenatally, thus representing the proportion of missed cases.

Table 2: Gender distribution among 78 fetuses with cleft lip (isolated and complex)

Cleft lip (n= 78)	Male	Female	Unknown	Male: Female
Isolated	3	3	2	1
Complex	1	1	0	1
Cleft lip and palate				
Isolated	28	18	2	1.56
Complex	9	10	1	0.9
Total	**41**	**32**	**5**	**1.28**

Table 3: Distribution of cases of CL ± P detected according to trimesters

	First Trimester (<14 weeks)	Second Trimester (14- 24 weeks)	Third Trimester (>24 weeks)	Unknown	Total
Antenatal diagnosis of CL ± P	2	98	15	1	116*
Isolated CL ± P	0	60	11	1	72
Complex CL ± P	2	38	4	0	44
CL ± P Delivered in KKH	0	58	11	1	70
Isolated CL ± P					
Complex CL ± P	0	49	6	1	56
*Excluded 8 cases who were noted to have clefts postnatally	0	9	5	0	14

In the subgroup of cases that underwent an anomaly scan from 18-23+6 weeks, there were 58 cases of CL ± P confirmed postnatally, giving a detection rate of 93.1% (54/58). Detection rate was higher in isolated CL ± P before 24 weeks compared to CL ± P with anomalies ([100.0% (46/46) vs 63.6% (8/12)]. Whilst 100% of CL ± P were detected at screening for the isolated CL ± P subgroup, 23.9% (11/46) had additional anomalies during screening that were not present in the post-natal examination, suggesting markers that may have regressed or were not clinically siginificant at birth. In cases of isolated CL ± P diagnosed before 24 weeks where parents opted for karyotyping, 95.8% (23/24) had normal karyotype, compared to 88.9% (8/9) of cases with complex CL ± P, despite a similar proportion of parents opting for invasive testing [60.0% (24/40) vs. 64.3% (9/14)].

The incidence of structural abnormalities varied with the anatomical type of cleft. Subgroup analyses found that anomalies were found in 27.4% (17/62) of unilateral CL ± P, 16.7% (2/12) in bilateral CL ± P, and 50.0% (2/4) in median CL ± P.

Missed diagnosis

Following the neonatology postnatal review, it was found that 8 cases of CL ± P were not picked up on the antenatal scans. Of the 8 cases, 5 of them had other more prominent (e.g. cardiac) anomalies that were detected at the anomaly scans, although CL ± P was not included as one of the anomalies. This highlights the challenge in detecting small CL±P especially in the presence of other more obvious anomalies

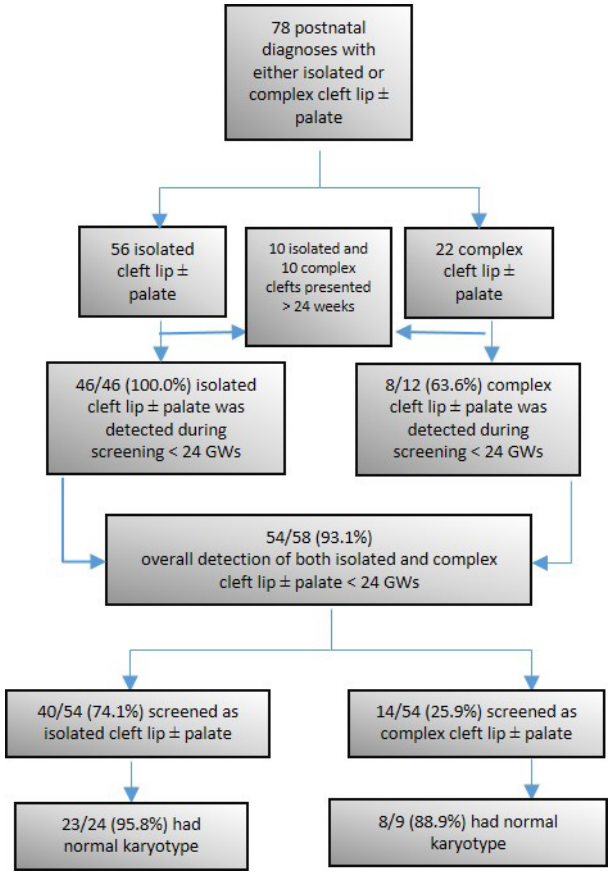

Figure 1: Postnatal clefts and proportion of karyotyping with abnormal results

Outcome

22 of cases were lost follow-up and outcomes of these pregnancies were not found within the national registry. It is surmised that they may have had their pregnancies terminated or delivered at overseas centres, thus negatively affecting the known live birth rate of the cohort.

Pregnancy outcomes in our study were comparable in both isolated CL ± P, and in complex CL ± P. In the subgroup of fetuses with isolated CL ± P, the live-birth rate was 87.5% (49/56) as compared to 86.4% (19/22) in the complex CL ± P group. Despite the comparable live-birth rates, the rate of neonate survival for the isolated CL ± P group was 100%, considerably higher than the complex CL ± P group's 81.0% (4/21, p=0.001).

Table 4: Outcomes of pregnancy

Outcomes of Pregnancy	% (n=124)
Live birth	58.9 (73)
Termination of pregnancy	18.5 (23)
Spontaneous miscarriage	1.6 (2)
Intrauterine demise	3.2 (4)
Loss to follow up	17.8 (22)

Discussion

Following advances in ultrasound technology and guidelines in standardization of care [11], CL ± P are being diagnosed antenatally with higher accuracy. Previous detection rates for CL ± P has ranged from 26% - 86%, with Ensing et al [12] reporting an improvement in detection rate of CL ± P from 43% before 2007 to 86% after 2007 following implementation of a national anomaly screening program.

It has been well established that detection rates are dependent on the nature of clefts and are higher when found in association with other anomalies. Clementi *et al.* [13] demonstrated that the overall detection rate for CL ± P was 26.8%, which was lower for isolated CL ± P (17.8%) but higher (44.4%) for CL ± P cleft with associated anomalies.

At this tertiary referral hospital in Singapore the antenatal detection rate before 24 weeks' gestation was 93.1%, which compares favourably with other well-established national prenatal screening programs [14]. The high detection rate before 24 weeks are likely due to the increased awareness and compliance to the anomaly scan service. There were no documented cases of refusal of the anomaly scan. In addition, these are performed by Fetal Medicine Foundation-certified sonographers with the requisite experience to recognize features of anomalies at an early stage of fetal development. We attribute a high detection rate due to increasing operator experience and use of adjunctive 3D ultrasound in suspected facial cleft. In the only 2 cases (1.6%) diagnosed early in the first trimester, CL ± P was detected alongside major associated anomalies. Both cases resulted in a termination of pregnancy. This suggests that in the absence of other obvious anomalies, isolated CL ± P may not be reliably detected in the first trimester. The late detection of 12.1% of clefts in the third trimester (15/124) was attributed to the late presentation for screening scans.

The prevalence in our local population is 13.6 per 10,000 live births. Retrospective review of past epidemiological studies conducted in Singapore (n=4) from 1983-2002, have shown that over a span of nearly three decades, this prevalence was thought to range from 18.7-20.7 per 10,000 live-births, which is above the Western population prevalence of 16-18 per 10,000 live-births [3-6]. The findings of this study, however, are at variance with previously published studies. The prevalence is in fact lower than the reported prevalence in Western studies, and in previous studies on the local population, despite the purported increased genetic predisposition amongst Asian populations. Factors that may have accounted for the lower prevalence include the benefits or pre-conception and antenatal folic acid use, which has now become a routine part of antenatal care, termination of fetuses with anomalies (including cleft) due to early detection early at the anomaly scan, and the number of cases (n=22) lost to follow-up, which the authors surmise to have had terminations or deliveries performed abroad. Nonetheless, this new figure represents an update to the existing body of locally derived data which is useful for counselling of affected parents, especially for parents receiving this diagnosis for the first time and therefore unfamiliar with this facial congenital abnormality.

In our study population comprising a multi-racial, multi-ethnic Asian population, the male to female ratio of fetuses with a cleft lip was 1.28. A review of published studies has shown that there is a preponderance of male fetuses (2:1) for cleft lips, but a 1:2 male to female ratio for clefts involving the palate only.

Authors of these studies have attributed this to the later closing of the palatine shelves in females compared to males [6,16,17]. Our study is consistent with the overall genetic disposition for affected male fetuses. However, the number of cases of isolated cleft palates (without cleft lip) was 0, and thus no meaningful comparison can be drawn.

Previous studies have published rates of associated anomalies for CL ± P from 35% to 63% [9]. Recent large studies such as the multicenter study by *Clementi et al* [13] showed that 27% of cases had one or more associated anomalies. This is consistent with data from The EUROCAT registry study, which noted associated anomalies in 29.2% of cases [18].

In cases of isolated CL ± P, there was no association with abnormal karyotypes [13-16]. However, in cases of CL ± P with associated structural abnormality, there was a substantially increased risk of a fetus having an underlying abnormal karyotype [17].

At our centre, the rate of CL ± P with one or more other anomalies was 28.2%, consistent with the previously mentioned rates of 27-29% [13-18]. Interestingly, we found that in cases of isolated CL ± P diagnosed before 24 weeks at our centre where parents opted for karyotyping, 95.8% revealed no abnormalities, compared to 88.9% of cases with abnormalities. This was despite a similar proportion of parents opting for invasive testing (60.0% vs 64.3%). It is note-worthy that overall in our population, the rate of karyotypic abnormalities range from 4.2-11.1%. This would provide greater consideration to parents who are weighing up the risks of invasive prenatal diagnostics versus the likelihood of detecting an abnormal karyotype based on antenatal scans.

The incidence of associated structural abnormalities has also been shown to vary with the anatomical type of cleft. Whilst median CL ± P make up about 1% of all clefts, they are often associated with other anomalies and hence a poorer prognosis [9,15]. Subgroup analyses in our study found that anomalies were found in 27.4% of unilateral CL ± P, 16.7% in bilateral CL ± P, and 50.0% in median CL ± P. The poor outcomes of median clefts were again seen in our study. Out of 4 cases of median cleft diagnosed at screening scan, 2 resulted in a termination (of which holoprosencephaly was found in one), 1 had an intrauterine demise at 38 weeks, and one was a stillbirth at 38 weeks with multiple fetal anomalies. This finding supports the earlier results of Fleurke-Rozema [15] which found that 100% of median CL ± P had anomalies. This highlights the need for accurate ultrasound diagnosis, in establishing the location and extent of the cleft lip, both for prognostication and to offer targeted chromosomal testing, especially in findings of median clefts. The strong association of median clefts with poor prognoses would warrant further counselling and a need for closer antenatal surveillance if pregnancy is continued.

Outcomes of pregnancy

Pregnancy outcomes in our study were comparable between isolated CL ± P and complex CL ± P. In the subgroup of fetuses with isolated CL ± P, the live-birth rate was 87.5% (49/56) as compared to 86.4% (19/22) in the complex CL ± P group. While the live-birth rates in both groups are comparable, neonates with isolated CL ± P had a higher survival rate (100% vs 81%, $p<0.001$, which raises the possibility of the effect of submicrosopic deletions and duplications on these pregnancies, thus highlighting the need to offer chromosomal microarray which has been the practice in centres such as those of Fleurke-Rozema et al. Ensing et al, and Mink et al, have published data that in case of isolated CL±P, parents opt for termination of pregnancy around 5% of the time [12,19]. At our centre, the termination rate was 12.5%. It remains to be seen whether this rate will change following increased awareness of clefts and improved counseling on the prognosis of this condition based on local data.

Conclusion

In conclusion, the prevalence of CL ± P in our local population is lower than published western data, which reported a higher prevalence rate amongst Asian populations. It is also lower than previous local epidemiological studies on facial clefts. Prognosis differs depending on the type of cleft. Despite a higher proportion of unilateral and bilateral clefts compared to median clefts, the latter has been associated with poor outcomes. Abnormal karyotypes were more common in complex clefts compared to isolated clefts. The newly updated incidence rates, results of previous karyotyping done for CL ± P and correlation between the anatomy of cleft and pregnancy outcomes will allow parents to better understand the prognoses of CL ± P and provide a basis for parents weighing up the risks of invasive prenatal diagnostics versus the likelihood of detecting an abnormal karyotype. It may further impact on their decision to continue with the pregnancy. This will be of value towards counseling in our local context.

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