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Incidence of facial clefts in Cambridge, United Kingdom

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SUMMARY The aim of this study was to determine the incidence of facial clefting in Cambridge, UK, using multiple resources of ascertainment and to relate the findings to antenatal ultrasound screening (AUS) detection rates.

AUS records from an obstetric ultrasound department, post-natal records from the regional craniofacial unit, and autopsy reports of foetuses over 16 weeks' gestational age from a regional pathology department from 1993 to 1997 were retrospectively reviewed. Cross-referencing between the three data sets identified all cases of facial clefts.

Of 23 577 live and stillbirths, 30 had facial clefts. AUS detected 17 of these. Sixteen of the 30 had isolated facial clefts. Others had associated anomalies, chromosomal defects, or syndromes. Percentages and confidence intervals were calculated from the above data. Twenty-one resulted in live births, seven terminations, and two foetal deaths. Overall, detection rate by AUS was 65 per cent [67 per cent isolated cleft lip, 93 per cent cleft lip and palate (CLP), and 22 per cent isolated cleft palate], with no false positives. The incidence of facial clefts was 0.127 per cent (95 per cent confidence interval 0.089–0.182 per cent); the incidence for isolated CLP was lower than previously reported: 0.067 per cent (0.042–0.110 per cent). With one exception, all terminations were in foetuses with multiple anomalies.

The figures presented will enable joint CLP clinics to give parents information of termination rates. The study allows pre-pregnancy counselling of families previously affected by clefting about the reliability of AUS detection rates.

Introduction

Previous studies on the prevalence of facial clefts are usually reported as affected births per 1000 live births. Data collection is usually retrospective and depends on information obtained from registries. Stillbirths, children dying at home, and terminations may be missed (Knox and Braithwaite, 1963), although more recent studies have included these (Hashmi *et al*., 2005). Earlier studies relied on the accuracy of post-natal reporting (McMahon and McKeown, 1953; Owens *et al*., 1985; Womersley and Stone, 1987; Coupland and Coupland, 1988; Jensen *et al*., 1988; Gregg *et al*., 1994). This is the first study in the UK taking the above issues into consideration.

Since the introduction of antenatal ultrasound screening (AUS) more accurate reporting of the incidence of foetal abnormalities is possible although detection rates vary considerably (Levi *et al*., 1991). There have been reports of high levels of terminations of pregnancies for isolated facial clefts in some countries (Bronshtein *et al*., 1994). This has led to renewed interest in the counselling pathway and the information supplied to parents. This study will help shed light on the reliability of AUS in the diagnosis of facial clefting. This is of particular interest when counselling parents with previous familiar facial clefting.

The purpose of this study was to determine the incidence of facial clefting in the Cambridge (UK) area and to ascertain the accuracy of AUS detection. The outcome of foetuses with facial clefts is reported and the question as to whether early detection leads to increased termination rates in isolated clefts is addressed.

Materials and methods

In Britain, all pregnant women are offered a detailed AUS examination at 18–20 weeks gestation. Addenbrooke's Hospital, Cambridge, supervises approximately 5000 deliveries per annum; women attending for routine antenatal care are offered two AUS examinations at 8–12 and 18–20 weeks of gestation. The hospital is the only provider of AUS services for the local population. Trained sonographers perform all AUS examinations with recourse to consultant staff whenever there is a potential problem. All examinations are completed before 24 weeks gestation.

This set-up allowed accurate cross-referencing of the three databases to exactly determine the case numbers of orofacial clefts arising from the unselected screened population of Cambridge.

The Craniofacial Unit and the Perinatal Pathology Department are regional centres accepting referrals from the whole region, in addition to the local population of Cambridge. All foetal and antenatal deaths are investigated at the Perinatal Pathology Department. All clefts are referred to the tertiary craniofacial unit. This set-up permitted accurate identification of all cases of facial clefts. However, due to the nature of a retrospective study, it was not possible to fully investigate population-specific factors that may influence incidence, such as drug history, social classification, and racial type.

The AUS records from the obstetric ultrasound (US) department, post-natal records from the regional craniofacial unit, and autopsy reports of foetuses over 16 weeks' gestational age from the regional pathology department over a 5 year period (1993–1997) were retrospectively reviewed. Cross-referencing of the three data sets identified 30 cases of facial clefts from the Cambridge area. Mathematical analysis of the data was by descriptive analysis and the confidence intervals were calculated (Altman, 1991).

Results

The results of the study are summarized in Table 1. Of 23 577 live and stillbirths and abortuses, 30 had facial clefts. The antenatal diagnoses, outcomes of pregnancy, and eventual diagnosis for these 30 cases are detailed in Table 1. The incidence of all facial clefts was 0.127 per cent [95 per cent confidence interval (CI) 0.089–0.182 per cent] or one in 786 (one in 551 to one in 1122) live, stillbirths, and terminations.

There were 22 765 live births, and 21 had facial clefts. The incidence for live births was 0.092 per cent (0.060–0.141 per cent) or one in 1084 (one in 709 to one in 1657). An overview of the outcome is shown in Table 2.

Four cases were excluded from analysis of AUS detection rates for the following reasons:

1. One baby had a small cleft of the soft palate and Beckwith–Wiedemann syndrome. This lesion was not detected ante- or post-natally until the child was 3 years old. As it is unlikely that this anomaly could have been detected antenatally, it was not included in the analysis for detection rates.
2. The mother of a baby born with a unilateral cleft lip and palate (CLP) presented late and the AUS was not performed until 29 weeks gestation. Limb and cardiac anomalies were seen but the face was difficult to examine because of foetal position. This case was excluded from analysis because the patient was examined beyond 24 weeks gestation.
3. Two miscarriages diagnosed at the detailed AUS examination were excluded because it is not standard practise to perform detailed AUS, where there is foetal demise.

AUS detected 17 of all cases. Sixteen of the 30 had isolated facial clefts. Others had associated anomalies, chromosomal defects, or syndromes. Twenty-one resulted in live births, seven terminations, and two foetal deaths. For the purpose of antenatal detection rates, four cases were excluded from analysis. Seventeen of the remaining 26 cases were detected by AUS (65 per cent), comprising 2/3 (67 per cent) of isolated cleft lip, 13/14 (93 per cent) of CLP, and 2/9 (22 per cent) with cleft palate. For five patients, the US diagnosis of the type of facial clefting was not completely accurate and the correct diagnosis was established post-mortem. All five cases showed severe anomalies which lead to termination of pregnancy and a facial deformity was suspected. There were no false-positive diagnoses.

Discussion

The absence of an understanding of the aetiology of orofacial clefts makes epidemiological investigation and monitoring important for research and public health reasons. Sayetta *et al*. (1989) reported the major methodological problems encountered in descriptive epidemiology of facial clefts and recommended use of multiple sources of ascertainment from population-based samples for incidence statistics. In preparing incidence data to support genetic or aetiologic studies, they suggested that all abortuses and stillbirths should be included.

This set-up in the present study permitted thorough and accurate interrogation and cross-referencing of three databases to extract cases of orofacial clefts arising from the unselected screened population of Cambridge.

From the cohort of 23 577 live and stillbirths and abortuses, the overall incidence of facial cleft was 0.127 per cent, which decreased to 0.092 per cent, when only live births were considered (prevalence). The incidence of clefts in this study is somewhat lower although still comparable with previously reported series (McMahon and McKeown, 1953; Czeizel and Tusnadi, 1971; Shaw *et al*., 1991; Gregg *et al*., 1994; Cooper *et al*., 2000; Rajabian and Sherkat, 2000; Mossey and Castillia, 2003; Harville *et al*., 2005; Hashmi *et al*., 2005; National Institute of Dental and Craniofacial Research, 2010). However, compared with other studies (Knox and Braithwaite, 1963; Owens *et al*., 1985; Womersley and Stone, 1987; Coupland and Coupland, 1988; Jensen *et al*., 1988; Antoszewski and Kruk-Jeromin, 1998; Christensen, 1999), the incidence rate is low. This may be explained by the small sample size and limited duration of the study or the difference may be due entirely to factors specific to the population screened. The general population of Cambridge consists mainly of middleclass white Caucasians, so racial differences (Vanderas, 1987; Mossey and Castillia, 2003) are unlikely to be the reason for the low incidence. The heightened awareness of neural tube defects by general medical practitioners and/or the

Table 1 Comparison of diagnosis at the 18–20 week antenatal anomaly ultrasound (US) with outcome of pregnancy and final clinical and pathological diagnosis

	Reported integrity of the lips and alveolus at the 18–20 week antenatal anomaly US	Outcome of pregnancy	Final clinical and pathological diagnosis
1	Normal	Live birth	Incomplete cleft soft palate in twin 2 of a multiple pregnancy
2	Normal	Live birth	Unilateral cleft lip
3	Normal	Live birth	Unilateral complete cleft lip and palate (CLP)
4	Normal	Live birth	Cleft palate
5	Normal	Live birth	Cleft palate, Pierre-Robin syndrome
6	Normal	Live birth	Cleft palate (mainly soft)
7	Normal	Live birth	Cleft soft palate
8	Unilateral cleft lip and alveolus	Live birth	Unilateral CLP
9	Unilateral cleft lip and alveolus	Live birth	Unilateral CLP, Turner's syndrome
10	Unilateral cleft lip and alveolus	Live birth	Unilateral CLP
11	Unilateral cleft lip and alveolus	Live birth	Unilateral CLP
12	Unilateral cleft lip and alveolus	Live birth	Unilateral CLP
13	Unilateral cleft lip	Live birth	Unilateral cleft lip
14	Incomplete unilateral cleft lip	Live birth	Incomplete unilateral cleft lip
15	Bilateral cleft lip and alveolus	Live birth	Bilateral CLP plus double aortic arch
16	Bilateral cleft lip and alveolus	Live birth	Bilateral CLP
17	Unilateral cleft alveolus	Live birth	Unilateral CLP, Opitz G/BBB syndrome
18	Left cleft lip and alveolus lip	Live birth	Left CLP and incomplete right cleft
19	Unilateral cleft alveolus	Live birth	Unilateral incomplete cleft lip and cleft submucous soft palate
20	Normal face	Termination	Cleft palate acrocephalosyndactyly, probable Aperts syndrome, but multiple other anomalies
21	Abnormal facial profile	Termination	Cleft palate. Renal hypoplasia, coarctation aorta. Normal karyotype 46, XX, and multiple anomalies
22	Midline defect	Termination	Cleft palate. Multiple dysmorphic features consistent with 4p- syndrome and multiple other anomalies
23	Normal face	Termination	Cleft palate. Complete situs inversus, hydrocephalus, small ventricular septal defect (VSD) normal karyotype 46, XY but other multiple anomalies
24	Bilateral cleft lip and alveolus	Termination	Bilateral CLP. Transposition of great vessels associated with pulmonary artery hypoplasia. VSD and multiple anomalies. Normal karyotype 46, XX
25	Bilateral cleft lip and alveolus	Termination	Bilateral CLP plus severe anomalies, Roberts syndrome and multiple anomalies
26	Bilateral cleft lip and alveolus	Termination	Bilateral CLP
27*	US diagnosis of foetal death, not screened for further abnormalities	Intrauterine death	Unilateral cleft lip
28*	US diagnosis of foetal death, not screened for further abnormalities	Intrauterine death	CLP, omphalocele, and abnormal facies
29*	Multiple limb and cardiac abnormalities, not screened for facial clefts, presented at 29 weeks	Live birth	CLP, cardiac and limb abnormalities
30*	Normal	Live birth	Bifid uvula, diagnosed at 3 years of age

*Not included in accuracy of US diagnosis.

Table 2 Outcome of facial clefts out of all pregnancies (live, stillbirth, and abortuses)

	%	N (L)	P	D (%)
Isolated cleft lip	10	3 (3)	0.0127	67
with other abnormalities	3	1 (0)	0.0042	
Isolated cleft lip and palate	30	9 (7)	0.0381	93
with other abnormalities	23	7 (4)	0.0296	
Isolated cleft palate	17	5 (5)	0.0212	22
with other abnormalities	17	5 (1)	0.0212	

N, all; L, live born; P, prevalence; D, detected by antenatal ultrasound, figure includes other anomalies.

population itself may have contributed to increase in dietary supplements of folic acid/vitamins by expectant mothers. A generally healthy lifestyle of a well-educated population with low rates for smoking and maternal alcohol use may also have been a contributing factor for the low incidence of facial clefting. These arguments, however, are only speculative and, due to the retrospective design of this study cannot be verified. The lower rate of cleft prevalence at birth could also be explained by the method of data collection, which cross-referenced three databases, thus avoiding potential double registration. It is of interest that the incidence for clefts decreased to 0.092 per cent, when only live births were considered. This supports the assertion

that failure to account for foetal wastage and under-ascertainment may have biased prevalence statistics (Sayetta *et al*., 1989). In the present cohort, there were major and minor abnormalities associated with 43 per cent of all clefts, which is comparable with statistics in the literature (Wyszynski *et al*., 1996). A number of pregnancies affected by additional defects were stillborn or terminated, which reduced the number of patient affected by facial clefting at birth (prevalence). Due to the small sample size, it was not possible to investigate seasonal variability of prevalence of facial clefting, which has been associated with use of pesticides and fungicides (Amidei *et al*., 1994; Garry *et al*., 2002; Krost and Schubert, 2006).

Studies by Bronshtein *et al*. (1996, 1994) reported high early AUS detection rates for facial clefts of which many resulted in termination of pregnancies. The current data does not support this as the experience in Europe is still that many isolated clefts detected pre-natally result in live births (Boyd *et al*., 1998; Blumenfeld *et al*., 1999; Jones, 1999). In the event, only one isolated CLP resulted in termination of pregnancy. It must be emphasized that prenatal US diagnosis of all facial clefts, however, remains low, at best 65 per cent. The reported high detection rate refers to the diagnosis of CLP rather than other types of orofacial clefts, the reason is that the sonologist or sonographer relies on identifying a defect in the maxillary alveolus, which alerts the operator to the presence of a cleft lip. Investigation of the maxillary alveolus is easily attainable unlike interrogation of the soft palate or the lip alone.

In the present climate of evidence-based medicine, it is important that professionals have data from pre- and post-natal studies from unselected populations to give parents to-be precise information about the incidence of facial clefting once these are detected antenatally. This study comes as close as possible to the true occurrence of oral clefts in 18–20 week old unborn foetuses and furthermore reports the accuracy of antenatal US of specific cleft types, i.e. there were no false positives in the cohort. It is important to have this data for counselling and it may help in the planning of service provision.

Conclusions

1. In this study, 43 per cent of foetuses affected by facial clefting had other anomalies, which nearly always led to termination of the pregnancy.
2. Facial clefting without other abnormalities led to termination of pregnancy in only one case.
3. Detection rate by AUS was highest for CLP (93 per cent), followed by cleft lip (67 per cent). An isolated cleft palate was the least likely to be detected by AUS. First detection of facial clefts at birth is hence most likely for isolated cleft palate patients. Diagnosis by AUS will form the majority new diagnoses for facial clefting. Once detected parents should ideally be counselled in antenatal joint clinics.
4. The prevalence of facial clefting at birth was low in the investigated sample. This information, if confirmed by future research, may be useful for planning of service provision.

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