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Prevalence of fetal facial cleft at different stages of pregnancy

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ABSTRACT

During a 7-year period (1988–94), we diagnosed 102 fetuses with trisomy 18, and 54 with trisomy 13; in 6.9% of the trisomy 18 and in 40.7% of the trisomy 13 fetuses, there was a facial cleft. On the basis of (1) these frequencies of facial cleft in trisomic fetuses; (2) the reported prevalence of facial cleft in mid-trimester fetuses; and (3) estimates of the prevalence of trisomies 18 and 13 at 20 weeks of gestation in a population with the maternal age distribution of all deliveries in England and Wales, it was calculated that 6.5% of fetuses with a facial cleft would have trisomy 18 or 13. This estimated frequency of trisomies was significantly lower than the 26% observed in 111 fetuses with a facial cleft that were referred to our unit for fetal karyotyping. These findings suggest that the patients with a facial cleft examined in a referral center are preselected in favor of those with multiple abnormalities, and therefore a higher frequency of associated chromosomal defects. In the future, with improving quality of ultrasound equipment and standards of scanning, it is likely that more cases of isolated facial cleft will be identified and, consequently, the observed frequency of chromosomal defects should decrease.

INTRODUCTION

The frequency of chromosomal defects in prenatally diagnosed abnormalities is much higher than that reported in neonates. For example, the mean frequency of trisomies 18 and 13 in fetuses with exomphalos is 36%, whereas in neonates with this abnormality the frequency of trisomies is only 9%[1]. In the case of conditions such as exomphalos, the most likely explanation for this apparent discrepancy is the high intrauterine lethality and selective termination of the chromosomally abnormal, compared to normal, fetuses. An additional factor is the preselection of patients in the postnatal series; these are mainly reported by neonatal surgical units that are unlikely to receive all neonates with highly lethal chromosomal defects[1].

Another fetal abnormality that has been associated with a high frequency of trisomies 18 and 13 is facial cleft, and in prenatal series the reported prevalence is 41%[2–6] (Table 1). In this condition, in addition to the high intrauterine lethality of trisomic fetuses and underreporting of trisomic neonates, another factor that may account for the high frequency of trisomies is patient preselection. In contrast to exomphalos, which is easy to diagnose at routine ultrasound examination, prenatal diagnosis of facial cleft is difficult and the majority of cases are missed. In two screening studies involving a total of 24 802 patients, the prevalence of facial cleft was 0.125%; routine ultrasound examination identified only 23% of the fetuses[7,8].

It could be postulated that there is preselection of those fetuses that are currently detectable by routine ultrasound examination in favor of those with multiple

Table 1 Reports on antenatally diagnosed facial cleft, providing data on gestational age at diagnosis (GA in weeks) and the frequency of chromosomal defects in the total group and in the subgroups with isolated facial cleft and those with additional abnormalities. 18, trisomy 18; 13, trisomy 13

			Chromosomal defects					
Authors	*n*	*GA*	*Total* (%)	*Isolated*	*Multiple*	*18*	*13*	*Other*
Saltzman *et al.* (1986)[2]	12	18–37	33	0/2	4/10	1	3	—
Hsieh *et al.* (1991)[3]	6	28–37	50	—	3/6	2	1	—
Benacerraf and Mulliken (1993)[4]	22	15–40	27	0/9	6/13	1	5	—
Nicolaides *et al.* (1993)[5]	64	17–37	48	0/8	31/56	10	15	6
Turner and Twining (1993)[6]	7	18–32	29	0/2	2/5	1	1	—
Total	111	15–40	41	0%	51%	15	25	6

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additional abnormalities (51% of the cases in Table 1) and therefore a higher frequency of associated chromosomal defects. The aim of this study was to test this hypothesis.

PATIENTS AND METHODS

The Harris Birthright Research Centre for Fetal Medicine is a referral center for fetal diagnosis and therapy. Demographic details and ultrasound findings are entered into a computer database at the time of scanning. All ultrasound examinations are performed transabdominally (5-MHz or 3.75-MHz curvilinear transducer) and in all cases a systematic search is made for any structural or biometrical abnormalities. The results of further investigations and pregnancy outcome are entered into the computer retrospectively. A computer search was made for all cases of facial cleft and all cases of trisomies 18 and 13 that were examined at 16–26 weeks of gestation.

Statistical analysis

The χ^2 test was used to determine the significance of the difference between observed and expected prevalence of trisomies 18 and 13 in fetuses with facial cleft at 20 weeks of gestation (the median gestation of our fetuses with facial cleft). The expected total number of trisomies 18 and 13 in a population of 100 000 pregnancies with the maternal age distribution of all deliveries in England and Wales in 1992[9] was calculated by multiplying the maternal age-related risk for these trisomies with the number of women in each age group[10]. The number of cases with facial cleft in each karyotype group was derived by multiplying the number in each group by the respective prevalence of facial cleft. It was assumed that, first, the overall prevalence of facial cleft in the second trimester of pregnancy was 0.125% (the result of the two ultrasound screening studies[7,8]), and, second, the frequencies of facial cleft in 20-week fetuses with trisomies 18 and 13 were 6.9% and 40.7%, respectively (the findings of this study).

RESULTS

Prevalence of chromosomal defects in fetuses with a facial cleft

During a 7-year period (1988–94), we diagnosed 111 fetuses with a facial cleft. The median maternal age was 29 years (range 16–44) and the median gestational age was 20 weeks (range 16–26). In 41 (37%) of the cases, the facial cleft was isolated and, in 70 (63%), there were multiple additional abnormalities. All fetuses with isolated facial cleft were chromosomally normal, whereas 39 of the 70 with additional abnormalities (55% or 35% of the total group) had chromosomal defects (seven cases of trisomy 18, 22 of trisomy 13, three of unbalanced translocation between chromosomes 13 and 14, and one each of trisomy 21, trisomy 22, partial trisomy 4q, deletion 21q, deletion 4p, inversion of chromosome 9 and triploidy.

During the first 4-year period of the study, in 25% of the fetuses with facial clefts there were no other detectable abnormalities and the overall frequency of chromosomal defects was 42%; in the subsequent 3 years, the proportion of fetuses with an isolated facial cleft doubled and the overall frequency of fetuses with chromosomal defects decreased (Table 2).

Prevalence of facial cleft in trisomic fetuses

In the same 7-year period, we diagnosed trisomy 18 in 102 fetuses and seven (6.9%) of these had a facial cleft; trisomy 13 was diagnosed in 54 cases and 22 (40.7%) had a facial cleft.

Expected prevalence in an unselected population

The numbers of all pregnancies and those with fetal trisomy 18 or 13 in each maternal age group, in a population of 100 000 pregnancies with the age distribution of all deliveries in England and Wales in 1992[9], are shown in Table 3. The estimated total numbers of fetuses with trisomy 18 or 13 were 36.5 and 13.7, respectively[10]. If 6.9% of fetuses with trisomy 18 and 40.7% of those with trisomy 13 have a facial cleft, the numbers of trisomic fetuses with a facial cleft would be 2.52 and 5.56, respectively (total 8.08). On the assumption that 0.125% of the 100 000 fetuses have a facial cleft[7,8] then 6.5% (8.08 divided by 125) of all fetuses with a facial cleft would be trisomic (Table 3).

The observed frequency of trisomy 18 or 13 in our 111 fetuses with a facial cleft (26%) was significantly higher ($\chi^2 = 15.7$, $p < 0.001$) than the expected frequency in a population with the maternal age distribution of all deliveries in England and Wales in 1992 (6.5%).

DISCUSSION

The data of this study demonstrate that the frequency of trisomies 18 or 13 in fetuses with facial cleft investigated in a tertiary referral center (26%) is much higher than the estimated prevalence (6.5%) in a population with the maternal age distribution of all deliveries in England and Wales. These findings support the hypothesis that the patients with facial cleft examined in a referral center are preselected in favor of those with multiple abnormalities and therefore a higher frequency of associated chromosomal defects.

Table 2 Findings in fetuses with a facial cleft that were referred to the Harris Birthright Research Centre for Fetal Medicine between 1988 and 1994

Period	*n*	*Isolated*	*Abnormal karyotype*
1988–91	57	14 (25%)	24 (42%)
1992–94	54	27 (50%)	15 (28%)
Total	111	41 (37%)	39 (35%)

Table 3 Estimates for the total number of fetuses with a facial cleft, the total number of fetuses with trisomy 18, the number of fetuses with trisomy 18 and a facial cleft, the total number of fetuses with trisomy 13 and the number with trisomy 13 and facial cleft at 20 weeks of gestation in an unselected population of 100 000 pregnancies

Maternal age (years)	*All pregnancies*		*Trisomy 18*		*Trisomy 13*	
	Total	*Cleft*	*Total*	*Cleft*	*Total*	*Cleft*
< 25	30 800	38.5	4.9	0.34	1.8	0.73
25–29	35 534	44.4	7.5	0.52	2.8	1.14
30–34	24 102	30.2	9.3	0.64	3.5	1.42
35–39	8 132	10.2	8.9	0.61	3.4	1.38
40–44	1 373	1.7	5.2	0.36	1.9	0.77
≥ 45	59	0.07	0.7	0.05	0.3	0.12
Total	100 000	125.0	36.5	2.52	13.7	5.56

The most likely explanation for patient preselection is failure to detect fetuses with isolated facial cleft in the routine ultrasound centers, rather than a positive policy of referring for further investigation only those with additional abnormalities. This is supported by our finding that, in the later years of the study, both the relative frequency of fetuses with isolated facial cleft increased and the prevalence of associated chromosomal defects decreased.

In fetal facial cleft, the frequency of chromosomal defects is related to the presence of additional structural and/or biometrical abnormalities; in our study, all fetuses with isolated clefts were chromosomally normal. In addition, the risk for chromosomal defects is related to both the maternal age and the gestational age of the population examined. Although the risk is also related to the type of facial cleft, being higher in those with a median defect[11], this information was not recorded in our database during the first years of the study.

This study has demonstrated that the frequency of chromosomal defects in fetuses with abnormalities, usually reported from referral centers, may not be representative of the true frequency in the general population, but may merely reflect the standard of ultrasound scanning and therefore the degree of preselection at the routine centers. In the future, with improving quality of ultrasound equipment and standards of scanning, it is likely that more cases of isolated facial cleft would be identified and, consequently, the observed frequency of chromosomal defects would decrease.

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