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Absent nasal bone at 11–14 weeks of gestation and chromosomal defects

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ABSTRACT

Objective *To examine the association between absence of the nasal bone at the 11–14-week ultrasound scan and chromosomal defects.*

Methods *Ultrasound examination was carried out in 3829 fetuses at 11–14 weeks' gestation immediately before fetal karyotyping. At the scan the fetal crown–rump length (CRL) and nuchal translucency (NT) thickness were measured and the fetal profile was examined for the presence or absence of the nasal bone. Maternal characteristics including ethnic origin were also recorded.*

Results *The fetal profile was successfully examined in 3788 (98.9%) cases. In 3358/3788 cases the fetal karyotype was normal and in 430 it was abnormal. In the chromosomally normal group the incidence of absent nasal bone was related firstly to the ethnic origin of the mother (2.8% for Caucasians, 10.4% for Afro-Caribbeans and 6.8% for Asians), secondly to fetal CRL (4.6% for CRL of 45–54 mm, 3.9% for CRL of 55–64 mm, 1.5% for CRL of 65–74 mm and 1.0% for CRL of 75–84 mm) and thirdly, to NT thickness, (1.8% for NT < 2.5 mm, 3.4% for NT 2.5–3.4 mm, 5.0% for NT 3.5–4.4 mm and 11.8% for NT ≥ 4.5 mm. In the chromosomally abnormal group the nasal bone was absent in 161/242 (66.9%) with trisomy 21, in 48/84 (57.1%) with trisomy 18, in 7/22 (31.8%) with trisomy 13, in 3/34 (8.8%) with Turner syndrome and in 4/48 (8.3%) with other defects.*

Conclusion *At the 11–14-week scan the incidence of absent nasal bone is related to the presence or absence of chromosomal defects, CRL, NT thickness and ethnic origin.*

INTRODUCTION

There is a high association between trisomy 21 and absence of the nasal bone at the 11–14-week ultrasound scan. In a study examining the fetal profile for presence or absence of the nasal bone in 701 fetuses before chorionic villus sampling at 11–14 weeks, the fetal profile was successfully examined in all cases and the nasal bone was found to be absent in 72.9% (43/59) of trisomy 21 fetuses and in 0.5% (3/603) of chromosomally normal fetuses[1]. The likelihood ratio for trisomy 21 for absent nasal bone was 146 (95% CI, 50–434) and for present nasal bone it was 0.27 (95% CI, 0.18–0.40). It was estimated that when screening for trisomy 21 by a combination of maternal age and fetal nuchal translucency (NT), inclusion of examination of the fetal profile for the presence or absence of nasal bone could increase the sensitivity from 75% to 93% for a fixed false-positive rate of 5%. Furthermore, if these ultrasound findings are combined with maternal serum free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein (PAPP-A) at 11–14 weeks the sensitivity could increase to 97% for a false-positive rate of 5%[2]. The results of a high association between trisomy 21 and absent nasal bone have been confirmed by three subsequent studies. Otano *et al.*[3] reported absent nasal bone in 3/5 (60%) trisomy 21 fetuses and in 1/175 (0.6%) chromosomally normal fetuses. Zoppi *et al.*[4] reported absent nasal bone in 19/27 (70%) trisomy 21 fetuses and in 8/5485 (0.2%) chromosomally normal fetuses. Orlandi *et al.*[5] reported absent nasal bone in 10/15 (67%) trisomy 21 fetuses and in 10/1000 (1.0%) chromosomally normal fetuses.

In this extended series of 3829 pregnancies undergoing first-trimester fetal karyotyping, we examine further the association between absent nasal bone and trisomy 21 as well as other chromosomal defects.

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METHODS

In 3829 pregnancies between January 2001 and January 2003 we prospectively examined the fetal profile for absence or presence of the fetal nasal bone during the routine 11–14-week ultrasound examination, carried out before chorionic villus sampling for fetal karyotyping. In all cases there was prior screening for chromosomal defects by a combination of maternal age and fetal NT[6] and after counseling the parents had elected to have invasive testing. The fetal profile was successfully examined and absence or presence of fetal nasal bone was recorded in 3788 cases (98.9%). The CRL was recorded during the examination and the ethnic origin (Caucasian, Afro-Caribbean, Asian, Chinese/Japanese) of the mother was noted for subsequent analysis. There were 3614 singleton, 76 twin, six triplet and one quadruplet pregnancies, in which all fetuses were examined.

For examination of the nasal bone, the image was magnified so that only the head and the upper thorax were included in the screen and a mid-sagittal view of the fetal profile was obtained. The angle between the ultrasound transducer and an imaginary line passing through the fetal profile was about 45° and the probe was gently tilted from one side to the other of the fetal nose. When these criteria are satisfied, three distinct lines are seen at the level of the fetal nose. The first two, which are proximal to the forehead, are horizontal and parallel to each other, resembling an 'equals sign'. The top line represents the skin and the bottom one, usually thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, almost in continuity with the skin, but at a higher level, represents the tip of the nose. All scans were carried out by sonographers with extensive experience in examining the nasal bone and this part of the examination was always completed within the 20 min allocated for the 11–14-week scan[7].

Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of the examination. The results of fetal karyotyping were also entered into the database when they became available.

Statistical analysis

Logistic regression analysis was used to examine the effect of maternal ethnic origin and fetal crown–rump length (CRL) and NT on the incidence of absent nasal bone in the chromosomally normal and trisomy 21 fetuses. Since the median NT increases with CRL, each measured NT was expressed as a difference from the normal median for the same CRL (delta value).

RESULTS

The median maternal age was 37 (range, 16–48) years, the median CRL was 64 (range, 45–84) mm, and the median gestational age was 12 (range, 11–14) weeks. Examination of the fetal profile was possible in 3788 (98.9%) cases and of these the nasal bone was absent in 93/3358 (2.8%) chromosomally normal fetuses, in 162/242 (66.9%) fetuses with trisomy 21 and in 62/188 (33.0%) with other chromosomal defects (Table 1). In the normal group, the incidence of absent nasal bone was similar in fetuses from singleton (87/3108) and in those from multiple pregnancies (6/157; Fisher's exact test, $P = 0.457$). The relationship between absent nasal bone and ethnic group, fetal CRL and fetal NT are shown in Tables 2, 3 and 4, respectively.

Logistic regression analysis (produced by backward stepwise conditional elimination method including the significant predictors only) demonstrated that in the chromosomally normal fetuses, significant independent prediction of the likelihood of absent nasal bone was provided by CRL, delta-NT and Afro-Caribbean ethnicity whereas in the trisomy 21 fetuses it was by CRL and delta-NT only (Tables 5 and 6). In normal fetuses, likelihood

Table 1 Incidence of absent nasal bone in chromosomally normal and abnormal fetuses

Karyotype	n	*Absent nasal bone* (n *(%))*
Normal	3358	93 (2.8)
Trisomy 21	242	162 (66.9)
Trisomy 18	84	48 (57.1)
Trisomy 13	22	7 (31.8)
Turner syndrome	34	3 (8.8)
XXX, XXY, XYY	15	1 (6.7)
Triploidy	11	0 (–)
Other	22	3 (13.6)
Total	3788	

Table 2 Incidence of absent nasal bone in chromosomally normal and trisomy 21 fetuses and likelihood ratio according to ethnic group

Ethnic group	*Trisomy 21* (n *(%))*	*Normal karyotype* (n *(%))*	*Likelihood ratio (95% CI) for trisomy 21*	
			Nasal bone absent	*Nasal bone present*
Total ($n = 3788$)	162/242 (67.0)	93/3358 (2.8)	24.2 (19.4–30.1)	0.34 (0.28–0.40)
Caucasian ($n = 3520$)	146/220 (66.4)	78/3125 (2.5)	26.6 (20.9–3.7)	0.34 (0.28–0.41)
Afro-Caribbean ($n = 91$)	7/9 (77.8)	8/77 (10.4)	7.2 (3.3–1.7)	0.25 (0.07–0.62)
Asian* ($n = 118$)	8/11 (72.7)	7/103 (6.8)	10.7 (4.7–2.2)	0.29 (0.10–0.61)
Chinese/Japanese ($n = 43$)	1/2 (50.0)	0/37 (–)	–	–
Mixed ($n = 16$)	–	0/37 (–)	–	–

*People originating from India, Pakistan, Bangladesh, Sri Lanka and Philippines.

Table 3 Incidence of absent nasal bone in chromosomally normal and trisomy 21 fetuses and likelihood ratio according to crown–rump length (CRL)

CRL (mm)	*Trisomy 21* (n *(%))*	*Normal karyotype* (n *(%))*	*Likelihood ratio (95% CI) for trisomy 21*	
			Nasal bone absent	*Nasal bone present*
Total ($n = 3788$)	162/242 (67.0)	93/3358 (2.8)	24.2 (19.4–30.1)	0.3 (0.3–0.4)
45–54	26/33 (78.8)	23/505 (4.6)	17.3 (11.1–26.6)	0.2 (0.1–0.4)
55–64	62/94 (66.0)	48/1235 (3.9)	17.0 (12.4–23.1)	0.4 (0.3–0.5)
65–74	58/79 (73.4)	17/1118 (1.5)	48.3 (29.7–78.4)	0.3 (0.2–0.4)
75–84	16/36 (44.4)	5/500 (1.0)	44.4 (17.7–110.5)	0.6 (0.4–0.7)

Table 4 Incidence of absent nasal bone in chromosomally normal and trisomy 21 fetuses and likelihood ratio according to nuchal translucency thickness (NT)

NT (mm)	*Trisomy 21* (n *(%))*	*Normal karyotype* (n *(%))*	*Likelihood ratio (95% CI) for trisomy 21*	
			Nasal bone absent	*Nasal bone present*
Total ($n = 3788$)	162/242 (67.0)	93/3358 (2.8)	24.2 (19.4–30.1)	0.3 (0.3–0.4)
< 95th centile	20/33 (60.6)	38/2142 (1.8)	34.2 (22.0–50.8)	0.4 (0.3–0.6)
2.5–3.4	36/62 (58.1)	30/889 (3.4)	17.2 (11.4–25.7)	0.4 (0.3–0.6)
3.5–4.4	32/42 (76.2)	10/200 (5.0)	15.2 (8.3–28.4)	0.3 (0.1–0.4)
4.5–5.4	19/31 (61.3)	4/59 (6.8)	9.0 (3.6–23.7)	0.4 (0.3–0.6)
≥ 5.5	55/74 (74.3)	11/68 (16.2)	4.6 (2.7–8.1)	0.3 (0.2–0.4)

Table 5a Logistic regression analysis for likelihood of absent nasal bone in chromosomally normal fetuses, looking at crown–rump length, nuchal translucency thickness and ethnic group

Variable	*Univariate analysis*			*Multivariate analysis*		
	Odds ratio	*95% CI*	P	*Odds ratio*	*95% CI*	P
Crown–rump length	0.941	0.919 to 0.964	< 0.0001	0.939	0.917 to 0.963	< 0.0001
Delta-nuchal translucency	1.427	1.292 to 1.576	< 0.0001	1.417	1.286 to 1.562	< 0.0001
Ethnic group						
Caucasian	0.282	0.159 to 0.500	< 0.0001	0.499	0.307 to 0.814	< 0.01
Afro-Caribbean	4.287	1.998 to 9.195	< 0.001	3.017	1.457 to 6.249	< 0.01
Asian	2.642	1.191 to 5.860	0.016	1.066	0.485 to 2.342	0.874

Table 5b Logistic regression analysis with a reduced model produced by backward stepwise conditional elimination method for likelihood of absent nasal bone in chromosomally normal fetuses

Variable	*Univariate analysis*			*Multivariate analysis*		
	Odds ratio	*95% CI*	P	*Odds ratio*	*95% CI*	P
Crown–rump length	0.941	0.919 to 0.964	< 0.0001	0.939	0.917 to 0.963	< 0.0001
Delta-nuchal translucency	1.427	1.292 to 1.576	< 0.0001	1.435	1.305 to 1.577	< 0.0001
Afro-Caribbean	4.287	1.998 to 9.195	< 0.001	5.888	2.692 to 12.881	< 0.0001

of having an absent nasal bone (% risk) = (odds/1 + odds) × 100, where odds = e^y and $Y = \log_e$ (odds) = $-0.194 + 1.773 \times$ (1 for Afro-Caribbeans and 0 for other ethnic groups) $- 0.062 \times$ CRL (in mm) $+ 0.361 \times$ delta-NT (in mm). Similarly, in trisomy 21 fetuses, $Y = 2.263 - 0.031 \times$ CRL (in mm) $+ 0.159 \times$ delta-NT (in mm). The likelihood ratio for trisomy 21 for absent nasal bone is derived by dividing the likelihood (%) in fetuses with trisomy 21 by that in normal fetuses.

DISCUSSION

The findings of this study confirm the high association between absent nasal bone and trisomy 21 as well as

Table 6a Logistic regression analysis for likelihood of absent nasal bone in trisomy 21 fetuses, looking at crown–rump length, nuchal translucency thickness and ethnic group

	Univariate analysis			*Multivariate analysis*		
Variable	*Odds ratio*	*95% CI*	P	*Odds ratio*	*95% CI*	P
Crown–rump length	0.968	0.939 to 0.999	0.043	0.969	0.940 to 1.001	0.055
Delta-nuchal translucency	1.177	1.029 to 1.347	0.018	1.176	1.027 to 1.346	0.019
Ethnic group						
Caucasian	0.658	0.230 to 1.879	0.434	1.376	0.628 to 3.015	0.425
Afro-Caribbean	1.75	0.355 to 8.625	0.492	2.273	0.614 to 8.406	0.219
Asian	1.325	0.342 to 5.136	0.684	2.092	0.598 to 7.313	0.248

Table 6b Logistic regression analysis with a reduced model produced by backward stepwise conditional elimination method for likelihood of absent nasal bone in trisomy 21 fetuses

	Univariate analysis			*Multivariate analysis*		
Variable	*Odds ratio*	*95% CI*	P	*Odds ratio*	*95% CI*	P
Crown–rump length	0.968	0.939 to 0.999	0.043	0.969	0.940 to 1	0.051
Delta-nuchal translucency	1.177	1.029 to 1.347	0.018	1.173	1.025 to 1.342	0.02

other chromosomal defects. Highly skilled sonographers can obtain good views for adequate examination of the nasal bone in about 99% of cases. The nasal bone is absent in about 3% of chromosomally normal fetuses, in two thirds of those with trisomy 21 and in one third of those with other chromosomal defects. The study has also demonstrated that the incidence of absent nasal bone is higher in fetuses of Afro-Caribbean origin than in Caucasians, that it decreases with increased fetal CRL and increases with increased fetal NT. In the calculation of an individual patient-specific risk for a chromosomal defect it is necessary to take into account these demographic and ultrasound findings.

The association between a sonographic marker and ethnic origin has been reported previously in relation to second-trimester nasal bone hypoplasia, which is commoner in Afro-Caribbeans than in Caucasians[8], and intracardiac echogenic foci, which are commoner in Asians than in Caucasians[9]. The inverse relation between absent nasal bone and CRL is likely to be a consequence of gestational age-dependent individual differences in the onset of ossification of the nasal bone. Since the incidence of absent nasal bone in normal fetuses is considerably higher at 11 than at 13 weeks, the likelihood ratio for trisomy 21 with absent nasal bone is considerably lower at 11 than it is at 13 weeks. The reverse is true for fetal NT, because the incidence of absent nasal bone increases with NT, and therefore the likelihood ratio for trisomy 21 with absent nasal bone is considerably higher for low than for high NT.

In screening for trisomy 21 the individual patient-specific risk is calculated by multiplying the background risk, which depends on maternal age and gestational age, with the likelihood ratio of the various screening tests. In the case of fetal NT, every measurement represents a factor which is multiplied by the background risk to calculate a new risk[6]. The larger the NT, the higher the likelihood ratio becomes and therefore the higher the new risk. In contrast, the smaller the NT measurement, the smaller the likelihood ratio becomes and therefore the lower the new risk. The new background risk, based on maternal age, gestational age and fetal NT for CRL, can then be multiplied by the positive or negative likelihood ratio, depending on the absence or presence, respectively, of the nasal bone. As shown in this study, the likelihood ratio for the nasal bone depends on ethnic origin, CRL and NT.

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