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Likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11–14-week scan

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KEYWORDS: chromosomal defects; first trimester; nasal bone; nuchal translucency; screening; trisomy 21; ultrasound

ABSTRACT

Objective *To update the likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11–14-week scan.*

Methods *Ultrasound examination of the fetal profile was carried out and the presence or absence of the nasal bone was noted immediately before karyotyping in 5918 fetuses at 11 to 13+6 weeks. Logistic regression analysis was used to examine the effect of maternal ethnic origin and fetal crown–rump length (CRL) and nuchal translucency (NT) on the incidence of absent nasal bone in the chromosomally normal and trisomy 21 fetuses.*

Results *The fetal profile was successfully examined in 5851 (98.9%) cases. In 5223/5851 cases the fetal karyotype was normal and in 628 cases it was abnormal. In the chromosomally normal group the incidence of absent nasal bone was related first to the ethnic origin of the mother, being 2.2% for Caucasians, 9.0% for Afro-Caribbeans and 5.0% for Asians; second to fetal CRL, being 4.7% for CRL of 45–54 mm, 3.4% for CRL of 55–64 mm, 1.4% for CRL of 65–74 mm and 1% for CRL of 75–84 mm; and third to NT, being 1.6% for NT ≤ 95th centile, 2.7% for NT > 95th centile–3.4 mm, 5.4% for NT 3.5–4.4 mm, 6% for NT 4.5–5.4 mm and 15% for NT ≥ 5.5 mm. In the chromosomally abnormal group there was absent nasal bone in 229/333 (68.8%) cases with trisomy 21 and in 95/295 (32.2%) cases with other chromosomal defects. Logistic regression analysis demonstrated that in the chromosomally normal fetuses significant independent prediction of the likelihood of absent nasal bone was provided by CRL, NT and Afro-Caribbean ethnic group, and in the trisomy 21 fetuses by CRL and NT. The likelihood ratio for trisomy 21 for absent nasal bone was derived by dividing the likelihood in trisomy 21 by that in normal fetuses.*

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 and ethnic origin.*

INTRODUCTION

The well-recognized characteristic of a small nose in patients with Down syndrome was first reported by Langdon Down in 1866[1]. An anthropometric study in 105 patients with Down syndrome at 7 months to 36 years of age reported that the nasal root depth was abnormally short in 49.5% of cases[2]. Recent radiological and sonographic studies have demonstrated that nasal hypoplasia is present from intrauterine life. In the combined data from four postmortem radiological studies in a total of 105 aborted fetuses with trisomy 21 at 12–25 weeks of gestation there was absence of ossification of the nasal bone in 32.4% and nasal hypoplasia in 21.4% of cases[3–6]. Sonographic studies at 15–24 weeks of gestation reported that about 65% of trisomy 21 fetuses have absent or short nasal bone[7–11].

The fetal nasal bone can be visualized by sonography at 11 to 13+6 weeks of gestation[12]. This examination requires that the image be magnified so that the head and the upper thorax only are included in the screen (Figure 1). A mid-sagittal view of the fetal profile is obtained with the ultrasound transducer held parallel to the direction of the nose. In the correct view there are three distinct lines. The first two lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an 'equal sign'. The top line represents the skin and the bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, almost in

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continuity with the skin, but at a higher level, represents the tip of the nose. When the nasal bone line appears as a thin line, less echogenic than the overlying skin, it suggests that the nasal bone is not yet ossified, and it is therefore classified as being absent (Figure 2).

In the combined data from eight studies at 11 to 13+6 weeks on a total of 13 733 fetuses the fetal profile was successfully examined in 13 350 (97.2%) cases and the nasal bone was absent in 140/10 787 (1.3%) chromosomally normal fetuses and in 207/306 (67.6%) fetuses with trisomy 21[12–19]. One of these studies, in 3829 pregnancies, found that the incidence of absent nasal bone decreased with fetal crown–rump length (CRL), increased with nuchal translucency (NT) and was substantially higher in Afro-Caribbeans than in Caucasians. Consequently, in the calculation of likelihood ratios in screening for trisomy 21 adjustments must be made for these confounding factors[19].

In this extended series of 5918 pregnancies undergoing first-trimester fetal karyotyping we examine further the relationships between absent nasal bone and trisomy 21, fetal CRL, NT and maternal ethnic origin.

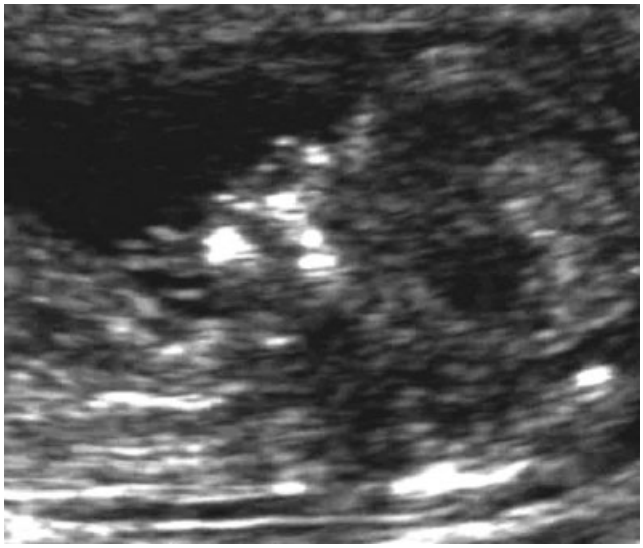

Figure 1 Nasal bone in a chromosomally normal fetus at 12 weeks.

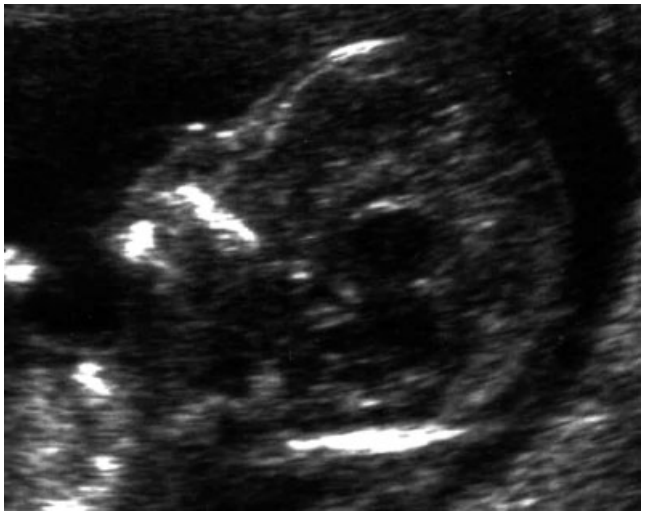

Figure 2 Absent nasal bone in a trisomy 21 fetus at 12 weeks.

METHODS

We prospectively examined 5918 fetuses for absence or presence of the nasal bone during the routine ultrasound examination at 11 to 13+6 weeks, carried out before chorionic villus sampling for fetal karyotyping between January 2001 and October 2003. There were 5602 singleton, 112 twin, seven triplet and one quadruplet pregnancies, in which all fetuses were examined. In all cases there was prior screening for chromosomal defects by a combination of maternal age and fetal NT[20] and after counseling the parents elected to have invasive testing. 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 time period allocated for the 11–14-week scan[21].

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

Statistical analysis

Logistic regression analysis was used to examine the effect of maternal ethnic origin, fetal CRL and fetal delta NT on the incidence of absent nasal bone in the chromosomally normal and trisomy 21 fetuses. The delta value is the difference between the observed NT and the normal median for the same CRL.

RESULTS

The median maternal age was 37 (range, 16–48) years, the median CRL was 65 (45–84) mm and the median gestation was 12.7 (11 to 13+6) weeks. Examination of the profile was possible in 5851/5918 (98.9%) fetuses and the nasal bone was absent in 129/5223 (2.5%) chromosomally normal fetuses, in 229/333 (68.8%) fetuses with trisomy 21 and in 95/295 (32.2%) with other

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

Karyotype	n	*Absent nasal bone (n (%))*
Normal	5223	129 (2.5)
Trisomy 21	333	229 (68.8)
Trisomy 18	124	68 (54.8)
Trisomy 13	38	13 (34.2)
Turner syndrome	46	5 (10.9)
XXX, XXY, XYY	20	1 (5.0)
Triploidy	19	0 (0)
Other*	48	8 (16.7)

*Mosaicism ($n = 23$), partial trisomy ($n = 12$), trisomy 22 ($n = 6$), unbalanced translocation ($n = 4$), deletion ($n = 3$).

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

Ethnic group	n	Trisomy 21 (n (%))	Normal karyotype (n (%))	LR (95% CI) for trisomy 21	
				Nasal bone absent	Nasal bone present
Total	5851	229/333 (68.8)	129/5223 (2.5)	27.8 (23.1–33.5)	0.32 (0.27–0.37)
Caucasian	5384	207/303 (68.3)	105/4811 (2.2)	31.3 (25.5–38.4)	0.32 (0.27–0.38)
Afro-Caribbean	170	11/14 (78.6)	13/145 (9.0)	8.8 (4.7–15.5)	0.24 (0.08–0.52)
Asian*	201	10/14 (71.4)	9/179 (5.0)	14.2 (6.8–28.4)	0.30 (0.12–0.58)
Chinese/Japanese	69	1/2 (50.0)	2/61 (3.3)	15.3 (2.1–73.4)	0.52 (0.10–0.94)
Mixed	27	—	0/27 (0)	—	—

*Individuals originating from India, Pakistan, Bangladesh, Sri Lanka and the Philippines. LR, likelihood ratio.

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

CRL (mm)	Trisomy 21 (n (%))	Normal karyotype (n (%))	LR (95% CI) for trisomy 21	
			Nasal bone absent	Nasal bone present
Total ($n = 5851$)	229/333 (68.8)	129/5223 (2.5)	27.8 (23.1–33.5)	0.32 (0.27–0.37)
45–54	41/49 (83.7)	32/675 (4.7)	17.6 (12.3–25.2)	0.17 (0.09–0.30)
55–64	78/118 (66.1)	63/1850 (3.4)	19.4 (14.7–25.5)	0.35 (0.27–0.44)
65–74	85/118 (72.0)	25/1805 (1.4)	52.0 (34.8–77.8)	0.28 (0.21–0.37)
75–84	25/48 (52.1)	9/893 (1.0)	51.8 (25.8–102.8)	0.48 (0.35–0.62)

CRL, crown–rump length; LR, likelihood ratio.

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

NT (mm)	Trisomy 21 (n (%))	Normal karyotype (n (%))	LR (95% CI) for trisomy 21	
			Nasal bone absent	Nasal bone present
Total ($n = 5851$)	229/333 (68.8)	129/5223 (2.5)	27.8 (23.1–33.5)	0.32 (0.27–0.37)
$\leq 95^{th}$ centile	23/38 (60.5)	53/3245 (1.6)	37.1 (25.0–52.5)	0.40 (0.26–0.56)
95th centile–3.4	48/83 (57.8)	40/1500 (2.7)	25.1 (16.7–37.4)	0.45 (0.34–0.56)
3.5–4.4	49/67 (73.1)	16/294 (5.4)	13.4 (8.2–22.1)	0.28 (0.19–0.41)
4.5–5.4	26/41 (63.4)	5/84 (6.0)	10.7 (4.6–25.3)	0.39 (0.25–0.55)
≥ 5.5	83/104 (79.8)	15/100 (15.0)	5.3 (3.4–8.7)	0.24 (0.16–0.34)

LR, likelihood ratio; NT, nuchal translucency.

chromosomal defects (Table 1). In the normal group the incidence of absent nasal bone was similar in fetuses from singleton (122/4991) pregnancies to that found for fetuses from multiple pregnancies (7/232; Fisher's exact test $P = 0.577$). The relationship between absent nasal bone and ethnic group, fetal CRL and fetal NT are shown in Tables 2–4.

Logistic regression analysis demonstrated that in the chromosomally normal fetuses significant independent prediction of the likelihood of absent nasal bone was provided by CRL, NT and Afro-Caribbean ethnic group, and in the trisomy 21 fetuses by CRL and NT (Tables 5–8). In normal fetuses the likelihood of having an absent nasal bone (%) = (odds/1 + odds)*100, where odds = e^y and $Y = \log_e$ (odds) = $-0.367 + 1.582 \times$ (1 for Afro-Caribbean and 0 for Caucasian, Asian, Oriental or mixed races) $- 0.061 \times$ CRL (in mm) $+ 0.349 \times$ delta NT (in mm). Similarly, in trisomy 21 fetuses, $Y = \log_e$(odds) = $2.275 - 0.032 \times$ CRL (in mm) $+ 0.207 \times$ delta NT (in mm). The likelihood ratio for trisomy 21 for absent nasal bone is derived by dividing the likelihood (%) in trisomy 21 by that in normal fetuses.

DISCUSSION

The findings of this study provide further evidence on the high association between absent nasal bone at the 11–14-week scan and trisomy 21 (Table 9). Trained sonographers can obtain good views for adequate examination of the nasal bone in about 99% of cases. The incidence of absent nasal bone is higher in fetuses of Afro-Caribbean origin than in Caucasians, it decreases with fetal CRL and increases with fetal NT. Consequently, in the calculation of an individual patient-specific risk for

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

	Univariate analysis			*Multivariate analysis*		
Variable	*OR*	*95% CI*	P	*OR*	*95% CI*	P
CRL	0.940	0.921–0.959	< 0.0001	0.941	0.922–0.960	< 0.0001
ΔNT	1.428	1.308–1.559	< 0.0001	1.408	1.296–1.531	< 0.0001
Ethnic group						
Caucasian	0.336	0.213–0.530	< 0.0001	0.486	0.227–1.038	0.062
Afro-Caribbean	4.213	2.315–7.666	< 0.0001	2.449	0.955–6.277	0.062
Oriental	1.344	0.325–5.561	0.6833	0.961	0.194–4.766	0.961

CRL, crown–rump length; ΔNT, delta nuchal translucency; OR, odds ratio.

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

	Univariate analysis			*Multivariate analysis*		
Variable	*OR*	*95% CI*	P	*OR*	*95% CI*	P
CRL	0.940	0.921–0.959	< 0.0001	0.941	0.922–0.961	< 0.0001
ΔNT	1.428	1.308–1.559	< 0.0001	1.418	1.306–1.540	< 0.0001
Afro-Caribbean	4.213	2.315–7.666	< 0.0001	4.863	2.630–8.991	< 0.0001

CRL, crown–rump length; ΔNT, delta nuchal translucency; OR, odds ratio.

Table 7 Logistic regression analysis for likelihood of absent nasal bone in trisomy 21 fetuses considering crown–rump length, nuchal translucency and ethnic group

	Univariate analysis			*Multivariate analysis*		
Variable	*OR*	*95% CI*	P	*OR*	*95% CI*	P
CRL	0.968	0.943–0.994	0.017	0.968	0.942–0.995	0.019
ΔNT	1.233	1.092–1.393	0.0007	1.232	1.091–1.392	0.0008
Ethnic group						
Caucasian	0.784	0.337–1.825	0.573	1.716	0.214–2.397	0.588
Afro-Caribbean	1.699	0.464–6.222	0.424	1.235	0.213–7.178	0.814
Oriental	0.452	0.028–7.293	0.576	1.394	0.019–8.031	0.545

CRL, crown–rump length; ΔNT, delta nuchal translucency; OR, odds ratio.

Table 8 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	*OR*	*95% CI*	P	*OR*	*95% CI*	P
CRL	0.968	0.943–0.994	0.017	0.968	0.942–0.995	0.019
ΔNT	1.233	1.092–1.393	0.0007	1.230	1.091–1.389	0.0008

CRL, crown–rump length; ΔNT, delta nuchal translucency; OR, odds ratio.

trisomy 21 it is necessary to take into account these demographic and ultrasound findings. The likelihood ratio for trisomy 21 with absent nasal bone is considerably higher in Caucasians than in those of Afro-Caribbean origin, it is lower at 11 than at 13 weeks and it is higher for low than for high NT.

It was previously estimated that if examination of the fetal profile for the presence/absence of the nasal bone is incorporated in first-trimester screening for trisomy 21 by fetal NT or NT and maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A the detection rates for trisomy 21 would

Table 9 Studies reporting on the association of absent nasal bone at the 11–14-week scan in chromosomally normal and in trisomy 21 fetuses

Reference	*Study*	*Successful examinations* (n (%))	*Absent nasal bone*	
			Normal (n (%))	*Trisomy 21* (n (%))
Cicero *et al.* (2001)[12]*	Pre-CVS	701/701 (100)	3/603 (0.5)	43/59 (72.9)
Otano *et al.* (2002)[13]	Pre-CVS	183/194 (94.3)	1/175 (0.6)	3/5 (60.0)
Zoppi *et al.* (2003)[14]	Screening	5525/5532 (99.8)	7/3463 (0.2)	19/27 (70.0)
Orlandi *et al.* (2003)[15]	Screening	1027/1089 (94.3)	10/1000 (1.0)	10/15 (66.7)
Viora *et al.* (2003)[16]	Screening	1752/1906 (91.9)	24/1733 (1.4)	8/10 (80.0)
Senat *et al.* (2003)[17]	Retrospective	956/1040 (91.9)	4/944 (0.4)	3/4 (75.0)
Wong *et al.* (2003)[18]	Pre-CVS	119/143 (83.2)	1/114 (0.9)	2/3 (66.7)
Cicero *et al.* (2003)[19]*	Pre-CVS	3788/3829 (98.9)	93/3358 (2.8)	162/242 (67.0)
Current study	Pre-CVS	5851/5918 (98.9)	129/5223 (2.5)	229/333 (68.8)
Total		15 413/15 822 (97.4)	176/12 652 (1.4)	274/397 (69.0)

*Data included in current study.

increase substantially and the false-positive rate would decrease[12,22]. For a fixed false-positive rate of about 5% the respective detection rates could increase from about 75% and 90% to 93% and 97%. For a fixed false-positive rate of about 1% the detection rates would be 57% for NT, 86% for NT and nasal bone and 93% for NT, nasal bone and serum biochemistry[12,22].

The likelihood ratios for absent or present nasal bone can be used by appropriately trained sonographers in the calculation of patient-specific risks for trisomy 21. However, it is imperative that, as for the NT scan, sonographers undertaking risk assessment by examination of the fetal profile must receive appropriate training and certification of their competence in performing the nasal bone scan. A study of 501 consecutively scanned fetuses by experienced sonographers reported that the fetal nasal bone could be successfully examined and measured in all cases without extending the length of time required for scanning[23]. Another study investigating the necessary training of 15 sonographers with experience in measuring fetal NT to become competent in examining the fetal nasal bone at 11–14 weeks has demonstrated that the number of supervized scans required is on average 80 with a range of 40–120[21].

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