Ultrasound Obstet Gynecol 2003; **21**: 15–18
Published online 18 December 2002 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.19

Nasal bone hypoplasia in trisomy 21 at 15–22 weeks' gestation

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KEYWORDS: absence of nasal bone; screening; second trimester; trisomy 21; ultrasonography

ABSTRACT

Objective *To investigate the potential value of ultrasound examination of the fetal profile for present/hypoplastic fetal nasal bone at 15–22 weeks' gestation as a marker for trisomy 21.*

Methods *This was an observational ultrasound study in 1046 singleton pregnancies undergoing amniocentesis for fetal karyotyping at 15–22 (median, 17) weeks' gestation. Immediately before amniocentesis the fetal profile was examined to determine if the nasal bone was present or hypoplastic (absent or shorter than 2.5 mm). The incidence of nasal hypoplasia in the trisomy 21 and the chromosomally normal fetuses was determined and the likelihood ratio for trisomy 21 for nasal hypoplasia was calculated.*

Results *All fetuses were successfully examined for the presence of the nasal bone. The nasal bone was hypoplastic in 21/34 (61.8%) fetuses with trisomy 21, in 12/982 (1.2%) chromosomally normal fetuses and in 1/30 (3.3%) fetuses with other chromosomal defects. In 3/21 (14.3%) trisomy 21 fetuses with nasal hypoplasia there were no other abnormal ultrasound findings. In the chromosomally normal group hypoplastic nasal bone was found in 0.5% of Caucasians and in 8.8% of Afro-Caribbeans. The likelihood ratio for trisomy 21 for hypoplastic nasal bone was 50.5 (95% CI 27.1–92.7) and for present nasal bone it was 0.38 (95% CI 0.24–0.56).*

Conclusion *Nasal bone hypoplasia at the 15–22-week scan is associated with a high risk for trisomy 21 and it is a highly sensitive and specific marker for this chromosomal abnormality. Copyright © 2002 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

In his original description of patients with trisomy 21, Langdon Down reported that the face was flat and the nose was small[1]. We have recently observed absence of the nasal bone in 2/3 trisomy 21 fetuses examined at 19–22 weeks of gestation[2]. We also reported that at 11–14 weeks' gestation the nasal bone is not visible by ultrasonographic examination in about 70% of fetuses with trisomy 21 and in less than 1% of chromosomally normal fetuses[3]. Furthermore, in trisomy 21 fetuses there was no significant difference in nuchal translucency thickness (NT) between those with and those without a visible nasal bone. Therefore, these two sonographic markers can be combined to provide a more effective method of early screening for trisomy 21, with an estimated detection rate of about 90% for a false-positive rate of 5%[3].

The aim of this study was to determine the incidence of absent nasal bone in chromosomally normal and abnormal fetuses at the mid-trimester scan and to investigate the potential value of this ultrasound marker in screening for trisomy 21.

METHODS

This was a prospective study in 1046 singleton pregnancies at 15–22 weeks' gestation conducted in two fetal medicine centers between January 2001 and October 2002. During the detailed ultrasound examination, which is routinely carried out before mid-trimester amniocentesis for fetal karyotyping, the fetal profile and nasal bone were also examined as described previously[2,3]. The nasal bone was considered to be hypoplastic if it was absent or it appeared strikingly small, in which case it was measured

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Accepted: 8 November 2002

and found to be always less than 2.5 mm (Figures 1–3). In a previous study of 367 fetuses reporting on nasal bone length, measured by ultrasonography in normal fetuses, the length increased with gestation from a mean of 4.7 mm at 15 weeks to 8.2 mm at 22 weeks and the respective values for the 2.5th centile were 3.2 and 6.0 mm[4]. In a recent study of 2050 normal fetuses at 15–22 weeks' gestation, the mean nasal bone length was 4.3 mm and the 2.5th centile was 2.8 mm at 15 weeks, and the respective values at 22 weeks were 7.5 and 5.6 mm[5]. 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

The incidence of nasal hypoplasia in the chromosomally normal and abnormal fetuses was determined and the likelihood ratios for trisomy 21 for the presence and hypoplasia of the nasal bone were calculated.

RESULTS

The median maternal age was 36 (range, 16–47) years and the median gestation was 17 (range, 15–22) weeks. The indications for amniocentesis were advanced maternal age (≥35 years) in 533 (51.0%) cases, maternal anxiety (of those <35 years) in 62 (5.9%), previous chromosomally abnormal pregnancy in six (0.6%), abnormal maternal serum biochemistry in 270 (25.8%) and abnormal ultrasound findings at a routine scan at the referring hospital in 175 (16.7%).

Examination of the fetal profile was possible in all cases and the nasal bone was hypoplastic in 21/34 (61.8%) fetuses with trisomy 21, in 12/982 (1.2%) chromosomally normal fetuses and in 1/30 (3.3%) fetuses with other chromosomal defects (Table 1). In the chromosomally normal group hypoplastic nasal bone was found in 4/870 (0.5%) Caucasians, 6/68 (8.8%) Afro-Caribbeans, 1/36 (2.8%) Asians and 1/8 (12.5%) Orientals (Table 2). In trisomy 21 there was no significant difference between those with present and those with hypoplastic nasal bone in median maternal age (37.5 vs. 37.8 years, Mann–Whitney *U*-test: $P = 0.924$) or gestational age (20 vs. 19 weeks, Mann–Whitney *U*-test: $P = 0.897$).

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

Fetal karyotype	n	*Nasal hypoplasia (%)*
Normal	982	12 (1.2)
Trisomy 21	34	21 (61.8)
Trisomy 18	14	1 (7.1)
Trisomy 13	5	0
Triploidy	4	0
Turner syndrome	6	0
47,XYY	1	0

Multiple fetal abnormalities were observed in all fetuses with trisomy 18, trisomy 13, triploidy and Turner syndrome. In the fetus with 47,XYY the fetal bowel was echogenic. In the chromosomally normal group, 694/982 (70.7%) fetuses had no abnormal ultrasound findings, 58 (5.9%) had at least one defect (heart defect ($n = 18$), diaphragmatic hernia (6), exomphalos (5), gastroschisis (1), facial cleft (6), hydrops (7), bilateral talipes (9), myelomeningocele (2), fetal akinesia deformation sequence (1), Dandy–Walker malformation (1), ventriculomegaly (1), polycystic kidneys (1), unilateral renal agenesis (1), ulnar aplasia (1)) and 230 (23.4%) had at least one chromosomal marker (choroid plexus cysts (45), mild cerebral ventriculomegaly with posterior horn diameter of 9–12 mm (28), increased nuchal fold thickness of at least 7 mm (11), intracardiac echogenic focus (81), dilated stomach (3), collapsed stomach (3), echogenic bowel (22), pyelectasis (30), short femur (32), hypoplastic middle phalanx of the fifth digit (7), sandal gap in the toes (3), pericardial effusion (3)), including 43/230 with at least two markers (Table 2).

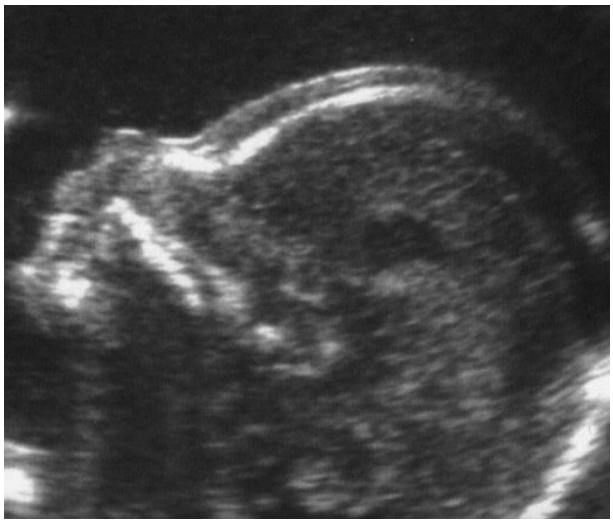

Figure 1 Fetal profile at 20 weeks' gestation in a normal fetus demonstrating the nasal bone.

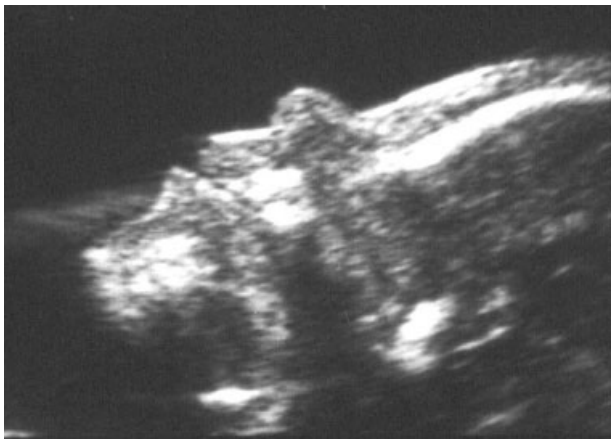

Figure 2 Fetal profile at 22 weeks' gestation in a trisomy 21 fetus demonstrating absence of the nasal bone.

Table 2 Incidence of hypoplastic nasal bone in trisomy 21 and chromosomally normal fetuses according to ethnic group and association with other ultrasound findings

	Trisomy 21 (n = *34*) *(%)*		*Normal karyotype* (n = *982*) *(%)*	
	Hypoplastic (n = *21*)	*Present* (n = *13*)	*Hypoplastic* (n = *12*)	*Present* (n = *970*)
Total ($n = 1016$)	21/34 (61.8)	13/34 (38.2)	12/982 (1.2)	970/982 (98.8)
Caucasian ($n = 898$)	17/28 (60.7)	11/28 (39.3)	4/870 (0.5)	866/870 (99.5)
Afro-Caribbean ($n = 72$)	3/4 (75.0)	1/4 (25)	6/68 (8.8)	62/68 (91.2)
Ultrasound defect ($n = 67$)	7/21 (33.3)	2/13 (15.4)	0/12	58/970 (6.0)
Chromosomal markers ≥ 2 ($n = 56$)	7/21 (33.3)	6/13 (46.1)	1/12 (8.3)	42/970 (4.3)
Chromosomal marker 1 ($n = 195$)	4/21 (19.1)	4/13 (30.8)	4/12 (33.3)	183/970 (18.9)
No abnormalities ($n = 698$)	3/21 (14.3)	1/13 (7.7)	7/12 (58.3)	687/970 (70.8)

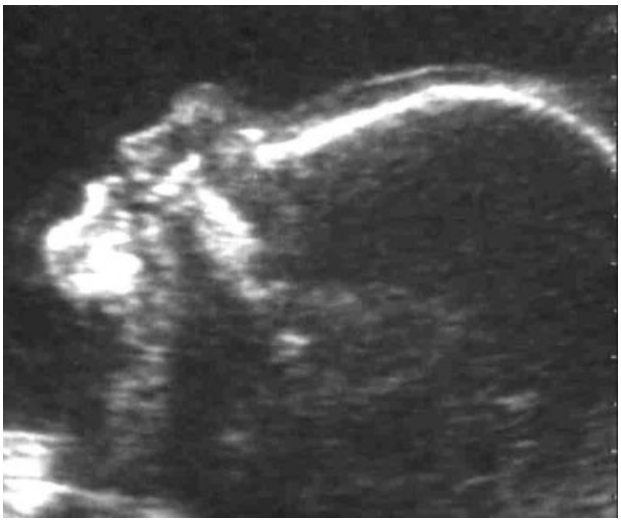

Figure 3 Fetal profile at 20 weeks' gestation in a trisomy 21 fetus demonstrating hypoplasia of the nasal bone.

In trisomy 21, 4/34 (11.8%) fetuses had no abnormal ultrasound findings, nine (26.4%) had at least one defect (heart defect (9), Dandy–Walker malformation (1)) and 21 (61.8%) fetuses had at least one chromosomal marker (choroid plexus cysts (1), mild cerebral ventriculomegaly (1), increased nuchal fold thickness of at least 7 mm (6), intracardiac echogenic focus (9), dilated stomach (3), echogenic bowel (3), pyelectasia (1), short femur (6), hypoplastic middle phalanx of the fifth digit (1), sandal gap in the toes (2), pericardial effusion (2)), including 13/21 with at least two markers.

In the 21 trisomy 21 fetuses with hypoplastic nasal bone the incidence of ultrasound defects, two or more chromosomal markers, one chromosomal marker and no abnormal ultrasound findings was seven (33.3%), seven (33.3%), four (19.1%) and three (14.3%), respectively. In the 13 with present nasal bone, two (15.4%) had ultrasound defects, six (46.1%) had two or more chromosomal markers, four (30.8%) had one chromosomal marker and one (7.7%) had no abnormal ultrasound findings.

The likelihood ratio for trisomy 21 for hypoplastic nasal bone was 50.5 (95% CI 27.1–92.7) and for present nasal bone it was 0.38 (95% CI 0.24–0.56). The likelihood ratios according to ethnic group and ultrasound findings are shown in Table 3.

Table 3 Likelihood ratio for trisomy 21 for hypoplastic and present nasal bone according to ethnic group and ultrasound findings

	Likelihood ratio for trisomy 21 (95% CI)	
Characteristic	*Hypoplastic nasal bone*	*Present nasal bone*
Total	50.5 (2.7–92.7)	0.39 (0.24–0.56)
Caucasian	132.1 (49.1–351.9)	0.39 (0.24–0.58)
Afro-Caribbean	8.5 (2.7–20.1)	0.27 (0.05–0.77)
Chromosomal markers ≥ 2	23.2 (4.1–136.5)	0.47 (0.24–0.72)
Chromosomal marker 1	23.4 (7.0–69.8)	0.51 (0.22–0.80)
No abnormalities	74.4 (24.2–169.4)	0.25 (0.05–0.71)

DISCUSSION

The data from this study demonstrate that hypoplastic nasal bone, found in about 1% of chromosomally normal fetuses, is a feature of about 60% of trisomy 21 fetuses at 15–22 weeks' gestation. These findings are similar to those of our previous study at 11–14 weeks' gestation, in which the nasal bone was absent in 73% of 59 trisomy 21 fetuses and in 0.5% of 603 chromosomally normal fetuses. In the 11–14 weeks' study the nasal bone was also absent in 11/20 fetuses with trisomy 18 and 2/8 with Turner syndrome but in the present study at 15–22 weeks the nasal bone was present in nearly all cases with these chromosomal defects. The study has also demonstrated racial differences in this sonographic finding with nasal bone hypoplasia in 0.5% of Caucasians and 8.8% of Afro-Caribbeans.

We found that a mid-trimester scan looking for hypoplastic nasal bone can potentially detect about 60% of trisomy 21 fetuses for a false-positive rate of 1%. Furthermore, the finding of nasal hypoplasia increases the a priori risk by about 50 times, whereas presence of the nasal bone reduces the risk to about half. If these findings are confirmed in prospective screening studies, then hypoplastic nasal bone would be the single most sensitive and specific second-trimester marker of trisomy

21. In screening for trisomy 21 by maternal age alone or maternal age and second-trimester maternal serum biochemistry the detection rates, for a fixed false-positive rate of 5%, are 30% and 65%, respectively[6].

Several studies in the last decade have reported on second-trimester sonographic markers of trisomy 21. In the combined data from two recent large series on a total of 350 trisomy 21 fetuses a major anomaly or a minor defect were detected in about 75% of affected fetuses and in about 13% of the chromosomally normal controls[7,8]. The respective detection and false-positive rates of screening for trisomy 21 using sonographic markers were 41.1% and 0.6% for increased nuchal fold thickness, 17.3% and 0.6% for echogenic bowel, 30.3% and 4.4% for intracardiac echogenic focus, 17.1% and 2.6% for pyelectasis, and 42.0% and 5.2% for short femur. In terms of the importance of isolated sonographic markers the respective sensitivity, false-positive rate and likelihood ratio for increased nuchal fold thickness were 4.7%, 0.5% and 9.4, for echogenic bowel were 1.7%, 0.5% and 3.4, for intracardiac echogenic focus were 6.4%, 3.9% and 1.6, for pyelectasis were 3.1%, 2.2% and 1.4, and for short femur were 5%, 3.9% and 1.3[7,8].

Currently the most effective method of screening for trisomy 21 is provided by a combination of maternal age, fetal NT and maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A at 11–14 weeks, which is associated with a detection rate of 90% for a false-positive rate of 5%[9,10]. It has also been estimated that if examination of the fetal profile for the presence/absence of the nasal bone is incorporated into first-trimester combined screening for trisomy 21 then the sensitivity would increase to 97%[11]. It is premature to speculate on the precise detection rates that could be achieved in the second trimester by a combination of maternal age, serum biochemistry and ultrasound examination for the fetal nasal bone and other sonographic markers. Nevertheless, the finding of our study, namely that nasal hypoplasia is likely to be the single most sensitive and specific second-trimester marker of trisomy 21, indicates that examination of the nasal bone will inevitably be incorporated into a sonographic or combined screening program for trisomy 21.

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