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Nasal bone assessment in prenatal screening for trisomy 21

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A small nose is a common facial feature of individuals with trisomy 21. Evidence based on radiologic, histomorphologic, and sonographic studies shows that nasal bone abnormalities are significantly more common in trisomy 21 fetuses than in euploid fetuses. These abnormalities, which include both nasal bone absence and short nasal bone length, can be detected by prenatal ultrasound. In this article we review the evidence and discuss the potential value of assessment of the fetal nasal bone in screening for trisomy 21.

In 1866 Langdon Down, reported that a small nose is one of the common facial features of individuals with the condition that subsequently came to bear his name.[1] Recently, a series of radiologic, histomorphologic, and sonographic studies have demonstrated that the nasal bone abnormality associated with trisomy 21 can be detected prenatally. In this article we review the evidence and discuss the potential value of assessment of the fetal nasal bone in screening for trisomy 21.

Nasal bone development

The nasal bones begin their development in the sixth week of gestation as collections of neural crest cells. Both nasal bones become ossified through the process of intramembranous ossification.[2-6] The earliest developmental stage at which the nasal bone can be demonstrated histologically is when the fetal crown-rump length (CRL) is 42 mm (10.9 weeks).[7]

The nasal bones develop as 2 separate structures with a gap in between them. The gap progressively narrows as the pregnancy progresses. However, even early in pregnancy, this gap has been shown not to have an impact on our ability to differentiate between nasal bone presence and absence using prenatal sonography.[8]

Anthropometric, radiologic, and histomorphologic evidence of nasal absence and hypoplasia in trisomy 21

An anthropometric study of 105 patients with trisomy 21 at 7 months to 36 years reported that the nasal root depth was abnormally short in about 50% of cases.[9]

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Table I Prevalence of nasal bone absence on x-ray films in terminated trisomy 21 fetuses

Author	N	Gestation (wks)	Absent nasal bone
Keeling et al[10]	31	12-24	8 (25.8%)
Stempfle et al[11,*]	31	15-23	11 (35.5%)
Tuxen et al[12]	33	14-25	10 (33.3%)
Larose et al[13]	21	13-25	10 (47.6%)
Total	116		39 (33.6%)

* Data presented here are limited to the second trimester.

In 4 postmortem radiologic studies in a combined total of 116 fetuses with trisomy 21 aborted at 12 to 25 weeks, there was absence of ossification of the nasal bone in 39 (33.6%) (Table I).[10-13] In addition, 1 of the studies examined the length of the nasal bone and reported this to be very short in 11 of the 23 (47.8%) trisomy 21 cases.[10] In the study by Tuxen et al[12] 8 of the 10 trisomy 21 fetuses with absent nasal bone had bilateral absence and in 2, the absence was unilateral. Seven of these fetuses had a histomorphologic evaluation, and the absence of nasal bone tissue was confirmed in all of them.

Ultrasound evidence of nasal hypoplasia in trisomy 21

In 2001 we described the technique for prenatal sonographic assessment of the fetal nasal bones and reported that in 2 of 3 fetuses with trisomy 21 the nasal bone was absent and in 1, it was hypoplastic (Figures 1 and 2).[14] An ultrasound image of a normal nasal bone in the second trimester is included for comparison (Figure 3).

Technique for evaluation the nasal bone

The nasal bones are 2 distinct structures and can be identified as such on ultrasound. For the evaluation to be valid, a strict set of rules needs to be followed.[15,16] This is especially true during the 11 to 13^{+6} week scan. The most important confounding variables are the presence of cartilaginous structures and bony structures within the fetal face other than the nasal bone and the fact that sonographically, the skin over the nasal bridge is quite echogenic in appearance, especially in the first trimester and the early part of the second trimester. The nasal bones are very thin elongated structures, which makes the angles of insonation used to evaluate these structures extremely important—the bones are usually easy to see if viewed along their long axis but difficult or impossible to visualize if viewed on end. With a few exceptions, the techniques for the nasal bone evaluation early in pregnancy (11-13^{+6} weeks' gestation) and later in pregnancy are very similar.

- The magnification of the fetus should be such that the head and the thorax occupy the whole image (11-13^{+6} week scan only).

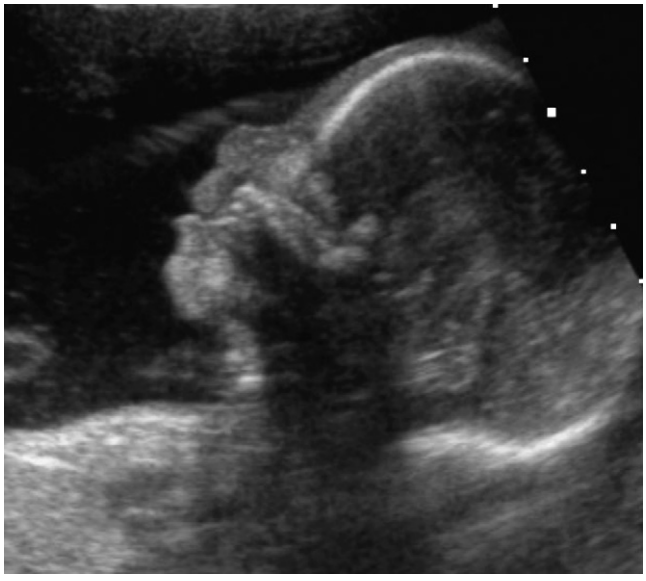

Figure 1 Fetal profile with an absent nasal bone in mid second trimester (trisomy 21).

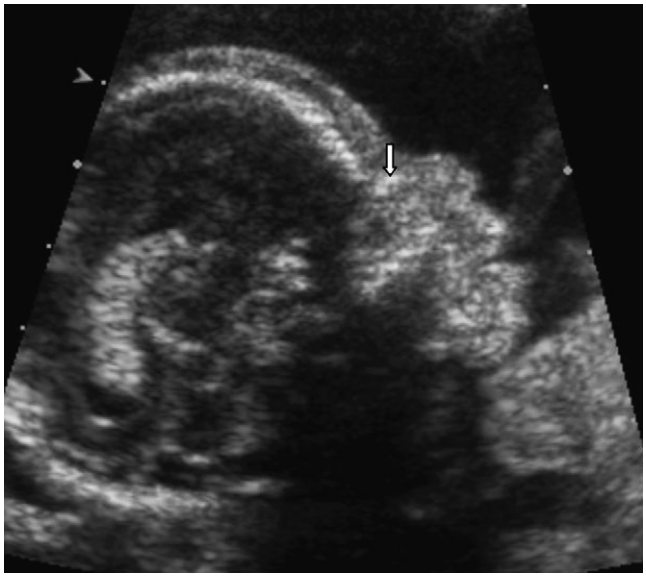

Figure 2 Fetal profile with a hypoplastic nasal bone (*arrow*) in mid second trimester (trisomy 21).

- The fetus needs to be facing the ultrasound transducer.
- A midsagittal view of the fetus needs to be obtained.
- For the purpose of simply identifying whether the nasal bone is present or absent, the face of the transducer should be parallel to the longitudinal axis of the nasal bone and to the skin over the nasal bridge (90-degree angle of insonation) (Figure 4). If the nasal bone is viewed "on end" (0-degree or 180-degree angle of insonation with respect to the longitudinal axis of the nasal bone), it will appear to be artificially absent

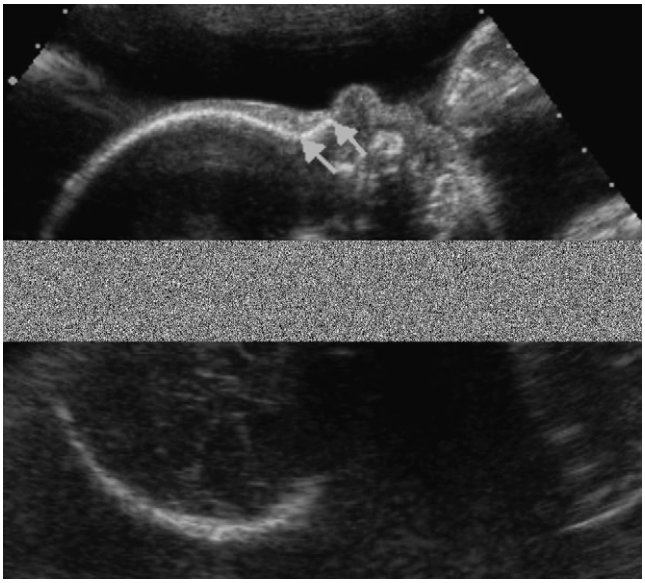

Figure 3 Fetal profile with a normal nasal bone in mid second trimester (euploid fetus). The *arrows* point to the proper placement of calipers for nasal bone measurement. Reprinted with permission from Bouley R, Sonek J. Fetal nasal bone: the technique. Down's Screening News 2003;10:33-4.

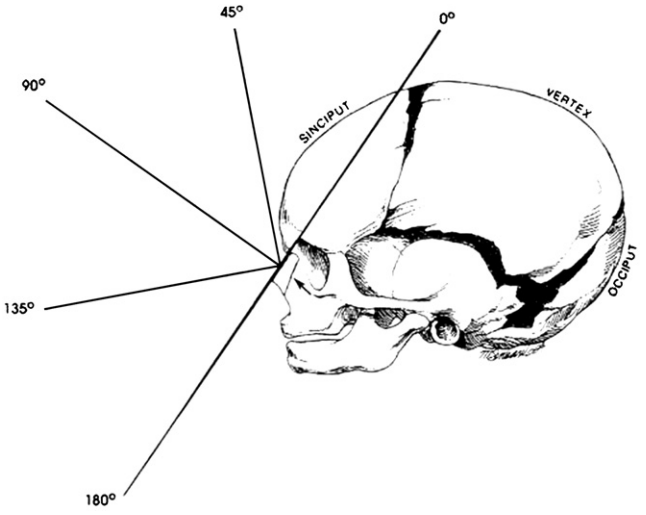

Figure 4 Diagrammatic representations of angles of insonation with respect to the longitudinal axis of the nasal bone (*arrow*). (Reprinted with modifications from Gabbe SG, Niebyl JP, Simpson JL, editors: Obstetrics: normal and problem pregnancies. 3rd ed. O'Brien WF, Cetalo RC. Labor and delivery, p. 393, 1996 with permission from Elsevier.

(Figure 5). This occurs because at this angle, the thinnest part of the nasal bone is being insonated. To measure the nasal bone in the second trimester, a slightly oblique angle (45 degree or 135 degree) will help to define the edges of the nasal bone more sharply (Figures 3).

• The following echogenic lines are important to identify in this view: the skin over the nasal bridge, a line below it that represents the nasal bone and is parallel to the nasal bridge skin, and an echogenic line that is further away from the forehead than the nasal bridge and at a slightly higher level that represents the skin over the nasal tip (Figure 6). The 2 parallel lines representing the skin over the nasal bridge and the nasal bone compose the so-called "equal sign." The line representing the nasal bone is thicker and more echogenic than the skin and usually contains a highly echogenic center. Both qualities need to be kept in mind to identify the nasal bone accurately. Tilting the transducer from side to side also helps to differentiate the skin from the nasal bone. Identification of all these landmarks is especially important during the 11 to 13^{+6} week scan. Goncalves et al[17] recently proposed absence of echoes originating from the frontal bones as an additional criterion for determining a precise midsagittal view. These echoes are absent because at this point in gestation the frontal bones are not yet fused in the midline.

If the bottom part of the equal sign is missing, the nasal bone is considered to be absent (Figure 7). Occasionally, a faint and slightly echogenic line that probably represents the nasal cartilage is seen within the nasal bridge. If this line is less echogenic than the skin or if only a small echogenic dot is seen, the nasal bone is also considered to be absent in most studies reported to date. The only exception is a recent study by Orlandi et al.[18] In this study, the nasal bone was considered absent if there was no evidence of a line below the nasal bridge skin at all.

• If the nasal bone is absent on ultrasound between 11 and 12 weeks' gestation, we recommend a repeat examination in 1 week. The result of the second examination should be the one used for risk evaluation. This approach reduces the false-positive rate.

• The obscuring effect and the presence of ossification centers within the fetal hands can produce confusing results if they are positioned in front of the fetal face, especially if they are actually resting on it.

The subtleties of the nasal bone evaluation, especially during the 11 to 13^{+6} week scan, require adequate training and experience before it can be accurately used. Cicero et al[19] studied the number of examinations required before sonographers became proficient in nasal bone evaluations. Fifteen sonographers, who were already trained to perform the 11 to 13^{+6} week scan, including the nuchal translucency measurement, were taught the technique of nasal bone evaluation. They found that the average number of studies required to achieve proficiency in nasal bone evaluation was 80 (40-120).

Absent nasal bone at 11 to 14 weeks

Several studies have demonstrated a high association between absent nasal bone at 11 to 13^{+6} weeks and trisomy 21, as well as other chromosomal abnormalities.

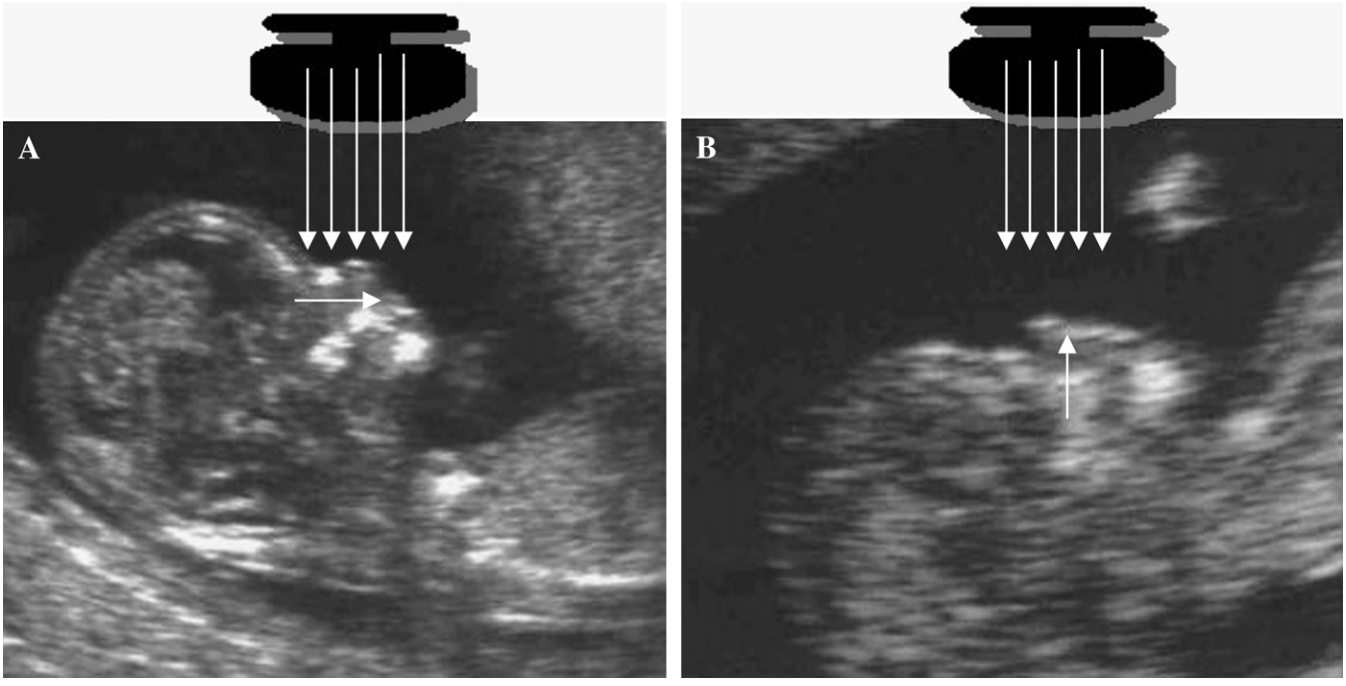

Figure 5 **A,** Correct angle of insonation (90 degrees) for detection of the nasal bone. **B,** The nasal bone is artificially absent because of a wrong angle of insonation (180 degrees). Reprinted with permission from Cicero S, Dezerega V, Andrade E, Scheier M, Nicolaides H. Learning curve for sonographic examination of the fetal nasal bone at 11-14 weeks. Ultrasound Obstet Gynecol 2003;22:135-7.

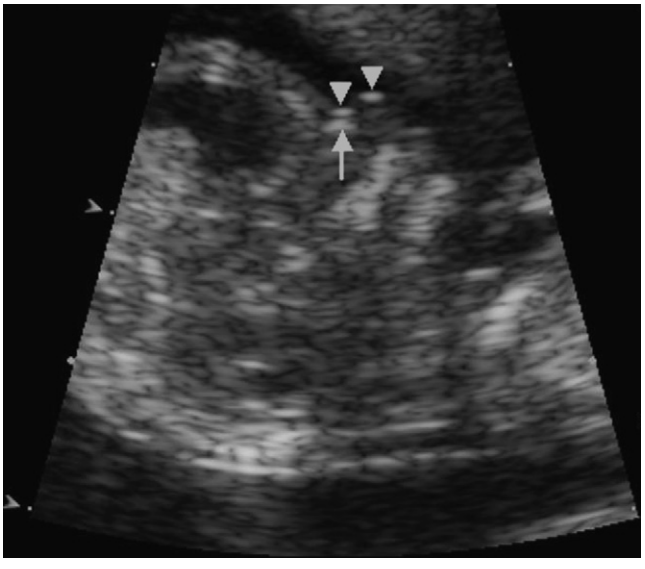

Figure 6 Fetal profile at 12 weeks' gestation with a normal nasal bone in an euploid fetus (nasal bone [*arrow*], skin lines over the nasal bridge and the nasal tip [*arrowheads*]). Reprinted with permission from Bouley R, Sonek J. Fetal nasal bone: the technique. Down's Screening News 2003;10:33-4.

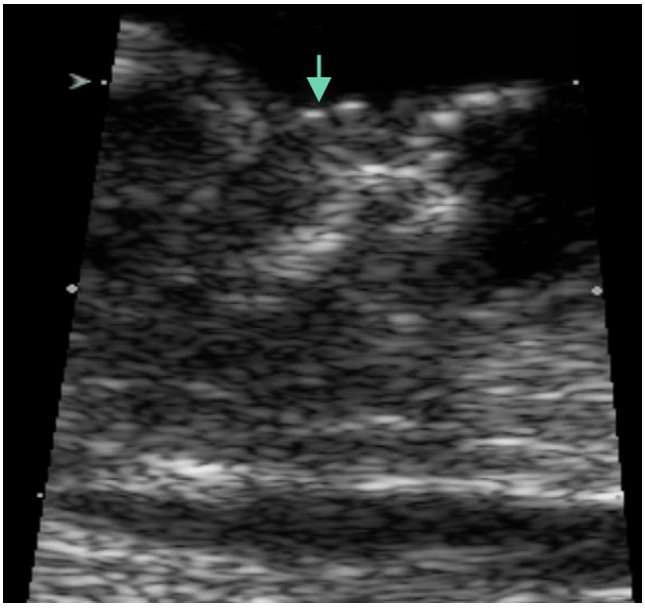

Figure 7 Fetal profile at 12 weeks' gestation with an absent nasal bone in trisomy 21. Note the absence of the equal sign. Only the echogenic skin line over the nasal bridge is seen (*arrow*). Reprinted with permission from Bouley R, Sonek J. Fetal nasal bone: the technique. Down's Screening News 2003; 10:33-4.

In the combined data from 8 studies, the fetal profile was successfully examined in 98.5% of the cases and the nasal bone was absent in 175 of 14,048 (1.2%) chromosomally normal fetuses and in 272 of 397 (68.5%) of fetuses with trisomy 21 (Table II).[18,20-28] Absence of the nasal bone has also been reported in about 55% of fetuses with trisomy 18, 35% of those with trisomy 13 and 10% with Turner syndrome.[28]

Table II Summary of available studies reporting on the prevalence of absent nasal bone in first-trimester trisomy 21 fetuses

Author	Study	Successful examination (n) (%)	Absent nasal bone	
			Normal (n) (%)	Trisomy 21 (n) (%)
Cicero et al[20,*]	Pre-CVS	701/701 (100%)	3/603 (0.5%)	43/59 (72.9%)
Otano et al[21]	Pre-CVS	183/194 (94.3%)	1/175 (0.6%)	3/5 (60.0%)
Zoppi et al[22]	Screening	5,525/5,532 (99.8%)	7/3,463 (0.2%)	19/27 (70.0%)
Orlandi et al[23]	Screening	1,027/1,089 (94.3%)	10/1,000 (1.0%)	10/15 (66.7%)
Viora et al[24]	Screening	1,752/1,906 (91.9%)	24/1,733 (1.4%)	8/10 (80.0%)
Senat et al[25]	Retrospective	956/1,040 (91.9%)	4/944 (0.4%)	3/4 (75%)
Wong et al[26]	Pre-CVS	119/143 (83.2%)	1/114 (0.9%)	2/3 (66.7%)
Cicero et al[27,*]	Pre-CVS	3,788/3,829 (98.9%)	93/3,358 (2.8%)	162/242 (67%)
Cicero et al[28]	Pre-CVS	5,851/5,818 (98.9%)	129/5,223 (2.5%)	229/333 (68.8%)
Orlandi et al[18]	Screening	2,411/2,411 (100%)	9/2,396 (0.4%)	8/15 (53.3%)
Total		16,797/17,044 (98.5%)	175/14,048 (1.2%)	272/397 (68.5%)

* The data in references 20 and 27 are included in Cicero et al[28] and some of the data in reference 23 are included in Viora et al.[24] The total numbers in the table exclude the data from references 20, 23, and 27.

Table III Prevalence of absent nasal bone in chromosomally normal and trisomy 21 fetuses and likelihood ratio according to CRL

CRL (mm)	Trisomy 21 (n) (%)	Normal karyotype (n) (%)	LR (95% CI) for trisomy 21	
			NB absent	NB 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)

Reprinted with permission from Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for Trisomy 21 in fetuses with absent nasal bone at the 11-14 weeks scan. Ultrasound Obstet Gynecol 2004;23:218-23.
NB, Nasal bone; *LR,* likelihood ratio.

Table IV Prevalence of absent NB in chromosomally normal and trisomy 21 fetuses and LR according to NT thickness

NT (mm)	Trisomy 21 (n) (%)	Normal karyotype (n) (%)	LR (95% CI) for trisomy 21	
			NB absent	NB present
Total (n = 5851)	229/333 (68.8)	129/5223 (2.5)	27.8 (23.1-33.5)	0.32 (0.27-0.37)
<95th	23/38 (60.5)	53/3245 (1.6)	37.1 (25.0-52.5)	0.40 (0.26-0.56)
>95th-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)

Reprinted with permission from Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for Trisomy 21 in fetuses with absent nasal bone at the 11-14 weeks scan. Ultrasound Obstet Gynecol 2004;23:218-23.

An additional important finding of this study was that the prevalence of absent nasal bone decreased with increasing fetal CRL (Table III), increased with nuchal translucency (NT) thickness (Table IV) and was substantially higher in Afro-Caribbean subjects than in white subjects (Table V).[28] Similarly, Prefumo et al[29] examined prospectively 3992 fetuses, and reported that the prevalence of nasal bone absence in fetuses whose mother was of African origin was 5.8%, in those of Asian origin it was 3.4% and in those of white origin, it was 2.6%. Consequently, these variables need to be taken into account when calculating likelihood ratios in screening for trisomy 21.

The data of all reported studies have been contradicted by the results of the FASTER trial, which included assessment of the nasal bone in 6316 fetuses scanned at 10 to 14 weeks' gestation.[30] Successful examination of the nasal bone was achieved in only 75.9% of the cases and the nasal bone was reported as present in all 9 of their fetuses with trisomy 21. The most likely explanation for these findings is that their technique for assessment of the nasal bone was not consistent with

Table V Prevalence of absent NB in chromosomally normal and trisomy 21 fetuses and LR according to ethnic group

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

Reprinted with permission from Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for Trisomy 21 in fetuses with absent nasal bone at the 11-14 weeks scan. Ultrasound Obstet Gynecol 2004;23:218-23.

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

Table VI Summary of studies reporting on the prevalence of absent NB in chromosomally normal and trisomy 21 fetuses in the second trimester

Study	Gestation (wks)	Prevalence of absent NB		LRs	
		Trisomy 21 fetuses	Euploid fetuses	Positive	Negative
Bromley et al[32]	15-20	6/16 (37.5%)	1/233 (0.4%)	93.8	0.63
Cicero et al[33]	15-22	11/34 (32.4%)	6/982 (0.6%)	54.0	0.68
Vintzileos et al[34]	18-20	12/29 (41.3%)	0/102 (0%)	—	—
Odibo et al[35]	15-22	5/18 (27.8%)	14/583 (2.4%)	11.6	0.74
Cusick et al[36]	16-19	1/4 (25%)	3/814 (0.4%)	69.4	0.75
Tran et al[37]	14-24	11/31 (35.5%)	1/136 (0.7%)	50.7	0.65
Benoit et al[38,*]	17-26	8/14 (57.1%)	0/18 (0%)	—	—
Total		54/146 (37.0%)	25/2868 (0.9%)	41.1	0.64

* Data presented here are limited to the second trimester.

that used by others. Furthermore, a report based on the quality assurance program of the FASTER trial revealed that a midsagittal plane was obtained in only 50% of the cases,[31] which would have made an accurate nasal bone assessment difficult.

Absent nasal bone at 15 to 24 weeks

Six studies examined the fetal profile for absence of the nasal bone before second-trimester genetic amniocentesis. In the combined data from these studies, the nasal bone was absent in 37% of the trisomy 21 fetuses and in 1% of the chromosomally normal fetuses (Table VI).[32-38] The overall likelihood ratio for an absent nasal bone was 41 and 0.64 for nasal bone presence. Further discussion regarding these studies is under the "Nasal bone length (NBL) in trisomy 21 at 15 to 24 weeks" section that follows.

Short nasal bone

Reference ranges of NBL

Several studies[32,36,37,39-43] have reported the measurement of NBL in normal fetuses. Their findings are summarized in Table VII, in which we present the estimated values for various percentiles at 12, 16, and 20 weeks to allow comparison between the studies. The 2.5th percentiles and 5th percentiles in the second trimester are fairly consistent from study to study, and it therefore appears reasonable to define nasal hypoplasia if the length is below 3 mm at 16 weeks and 4.5 mm at 20 weeks. The first-trimester data show a more significant divergence. The most likely explanation for this is that the technique used in theses studies was different. The reference ranges based on a measurement that includes both the hyperechoic central part of the nasal bone and the echogenic extensions at each end result[23,40] in measurements that are greater than the ones in which the hyperechoic center only is measured.[36,42]

NBL in trisomy 21 at 11 to 13^{+6} weeks

Measuring the NBL in the first trimester has thus far not been shown to benefit screening for trisomy 21. Cicero et al[42] examined 25 fetuses with trisomy 21 with an identifiable nasal bone between 11 and 13^{+6} weeks' gestation. They found that even though the NBL in these fetuses tended to be short for CRL, it was not significantly different from normal. Orlandi et al[23] found that the NBL in all 5 trisomy 21 fetuses with a detectable nasal bone was below the 50th percentile of the normal range. However, the degree of deviation from normal was too small for this measurement to be useful in screening for trisomy 21.

Table VII NBL measurements and percentiles at 12, 16, and 20 weeks' gestation based on data in euploid fetuses

		NBL (mm)											
		12 wks (percentiles)				16 wks (percentiles)				20 wks (percentiles)			
Author	N (total)	2.5th	5.0th	10th	50th	2.5th	5.0th	10th	50th	2.5th	5.0th	10th	50th
Guis et al[39]	376	—	—	—	—	3.1	—	—	5.2	5.7	—	—	7.6
Sonek et al[40]	3547	1.7	1.8	—	2.8	3.2	3.4	—	4.7	5.0	5.2	—	6.7
Orlandi et al[23]	1000	—	—	2.1	2.6	—	—	—	—	—	—	—	—
Bunduki et al[41]	1609	—	—	—	—	3.7	4.1	—	5.9	4.8	5.2	—	7.0
Cicero et al[42]	955	—	1.2	—	1.5	—	—	—	—	—	—	—	—
Cusick et al[36]	799	—	—	1.4	1.9	—	—	3.3	4.1	—	—	5.1	6.2
Bromley et al[32]	223	—	—	—	—	3.4	3.6	3.9	4.7	—	—	—	—
Tran et al[37]	136	—	—	—	—	3.1	—	—	3.4	4.9	—	—	5.2
Gamez et al[43]	1899	—	—	—	—	—	—	—	—	5.3	—	—	6.3
Ranges (mm)		1.7	1.2-1.8	1.4	1.5-2.8	3.1-3.7	3.1-4.1	3.3-3.9	3.4-5.9	4.8-5.3	5.2-5.7	5.1	5.2-7.6

Table VIII Summary of data from 2D ultrasound studies comparing the prevalence of NB abnormalities in trisomy 21 and in euploid fetuses

		Abnormal NB			LR	
Study	Gestation (wks)	Definition	Trisomy 21	Normal	Positive	Negative
Bromley et al[32]	15-20	Short	5/10 (50.0%)	10/222 (4.5%)	11.1	0.52
		Absent or short	11/16 (68.8%)	11/223 (4.9%)	14.0	0.32
Cicero et al[33]	15-22	Short	10/23 (43.5%)	6/976 (0.6%)	72.5	0.56
		Absent or short	21/34 (61.8%)	12/982 (1.2%)	51.5	0.39
Bunduki et al[41]	16-24	Short	13/22 (59.1%)	82/1,600 (5.1%)	11.6	0.43
Gamez et al[43]	19-22	Short	5/5 (100%)	34/1899 (1.8%)	55.6	—
Tran et al[37]	14-24	Short	4/20 (20.0%)	4/135 (3.0%)	6.7	0.82
		Absent or short	15/31 (48.4%)	5/136 (3.7%)	13.1	0.53
Cusick et al[36]	16-19	Short	3/3 (100%)	0/811 (0%)	—	—
		Absent or short	4/4 (100%)	3/814 (0.36%)	278	—
Total		Short	40/83 (48.2%)	136/5643 (2.4%)	20.1	0.53
		Absent or short	51/85 (60.0%)	31/2155 (1.4%)	42.8	0.40

NBL in trisomy 21 at 15 to 24 weeks

Six studies have compared the length of the nasal bone in trisomy 21 and normal fetuses (Table VIII).[32,33,36,37,41,43] In the combined data, the nasal bone was short in 40 of 83 (48.2%) trisomy 21 fetuses and 136 of 5643 (2.4%) normal fetuses. The studies essentially used 1 of 3 methods to define nasal bone hypoplasia: first, a measurement below the 2.5th, 5th, or 10th percentile of the normal range for gestation[41,43]; second, a measurement below a fixed cutoff of 2.5 mm or 3 mm[33,36]; and third, a ratio above specific cutoffs in the ratio of the biparietal diameter to NBL ratio.[32,37] The only study[33] that addresses the difference in the prevalence of nasal bone hypoplasia in the normal population based on ethnicity showed that it is much more common in Afro-Caribbean subjects (8.8%) than in white subjects (0.5%).

The combined prevalence of nasal bone absence and hypoplasia at 14 to 25 weeks' gestation is 60% in fetuses with trisomy 21 and 1.4% in euploid fetuses. Therefore, the combination of nasal bone absence and hypoplasia, if confirmed by further studies, may prove to be one of the strongest ultrasound markers for trisomy 21. It should be remembered that, for example, second-trimester serum screening using the combination of maternal age, human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), and estriol yields approximately the same detection rate with a 3.6× greater false-positive rate.

Three-dimensional ultrasound assessment of the nasal bones

Three-dimensional (3D) ultrasound studies published over the past 3 years have confirmed that there is a major difference in the prevalence of nasal bone absence in trisomy 21 fetuses and euploid fetuses. They also showed that this phenomenon is present in all 3 trimesters of pregnancy. The main advantages of a 3D ultrasound evaluation are that multiplanar imaging allows the

Table IX Second- and third-trimester 3D ultrasound studies comparing the prevalence of NB abnormalities in trisomy 21 and euploid fetuses

Study	Gestation (wks)	NB abnormality	Prevalence	
			Trisomy 21	Normal karyotype
Lee et al[45]	16-30	Absence (examiner 1)	8/20 (40.0%)	2/20 (10.0%)
		Absence (examiner 2)	9/20 (45.0%)	4/20 (20.0%)
Goncalves et al[46]	19-25	Absence	9/26 (34.6%)	1/27 (3.7%)
Benoit et al[38]	17-33	Bilateral absence	6/20 (30.0%)	0/18 (0%)
		Unilateral absence	3/20 (15.0%)	0/18 (0%)
		Either uni- or bilateral absence	9/20 (45.0%)	0/18 (0%)
Total	16-33	Absence	28/66 (42.4%)	4/65 (6.1%)

NB abnormalities in trisomy 21 and euploid fetuses.

operator to establish a true midsagittal view and that the angles of insonation can be optimized. It also improves our ability to evaluate each nasal bone individually.

The 11 to 13^{+6} week scan (3-D)

Rembouskos et al[44] showed that a 3D multiplanar imaging can be used to evaluate the fetal nasal bones at 11 to 13^{+6} weeks' gestation. However, to obtain a good quality volume, the same criteria as for a 2D nasal bone assessment have to be met, ie, the fetus had to be viewed in a midsagittal section facing the transducer and the correct angle of insonation had to be used. With the use of 3D ultrasound, Peralta et al[8] detected a gap between the 2 nasal bones in approximately 20% of fetuses at 11 to 13^{+6} weeks. They also demonstrated that if the gap exceeded 0.6 mm, the nasal bone would appear to be absent in a reconstructed perfectly midsagittal plane. This suggests that 0.6 mm is the limit of the lateral resolution of the ultrasound equipment. However, none of the fetuses were falsely diagnosed with nasal bone absence on 2D ultrasound. This demonstrates that the presence of a gap does not increase the false-positive rate.

Second and third trimester (3-D)

In a report by Lee et al,[45] 2 independent examiners evaluated 3D images of 20 fetuses with trisomy 21 and 20 fetuses with normal chromosomes. The prevalence of bilateral nasal bone absence in the trisomy 21 fetuses was found to be 40% and 45% by examiner 1 and examiner 2, respectively. These findings are similar to those on 2D ultrasound. However, the prevalences of nasal bone absence in the euploid fetuses reported by the same 2 examiners were 20% (4/20) and 10% (2/20), which is substantially higher than what the 2D and other 3D studies have reported.

Benoit and Chaoui[38] compared the 3D and 2D appearance of the nasal bone at 17 to 33 weeks. The nasal bone was present in all 18 euploid fetuses on 2D ultrasound and all were found to have both nasal bones present on 3D ultrasound. In the 20 fetuses with trisomy 21, 9 had either an absent or hypoplastic nasal bone on 2D ultrasound. The 3D evaluation showed bilateral nasal bone absence in 6 fetuses and unilateral nasal bone absence in 3. Goncalves et al[46] analyzed 3D volumes of the nasal bone at 20 to 25 weeks. Nasal bone absence was detected in 9 of 26 (34.6%) of the trisomy 21 fetuses and in 1 of 27 (3.7%) of the euploid fetuses.

The combined data of the three 3D studies (Table IX) estimates the prevalence of nasal bone absence in the second-trimester trisomy 21 fetuses at 42% and the prevalence of nasal bone absence in the euploid fetuses at 6%. The prevalence of nasal bone absence in the chromosomally normal fetuses is probably skewed by the much higher than expected prevalence in 1 of the studies.[45]

Inclusion of nasal bone evaluation in prenatal screening for trisomy 21

First-trimester screening

Effective screening for trisomy 21 and all major chromosomal defects can be achieved at 11 to 13^{+6} weeks by a combination of maternal age, fetal NT thickness, and maternal serum free ß-hCG and pregnancy-associated plasma protein A (PAPP-A). Prospective screening studies have demonstrated that for a false-positive rate of 5% the detection rate of trisomy 21 is about 90%.[47]

A case-control study comprising of 100 trisomy 21 and 400 chromosomally normal singleton pregnancies at 11^{+0} to 13^{+6} weeks of gestation found that the ultrasound finding of either the presence or absence the nasal bone is independent of serum free β-hCG and PAPP-A levels.[48] Therefore, the nasal bone evaluation can be added to the combination of NT and maternal serum free ß-hCG and PAPP-A measurements at 11^{+0} to 13^{+6} in screening for trisomy 21. Through mathematical modeling, it was estimated that for a false-positive rate of 5%, the potential detection rate of trisomy 21 would be more than 95%.

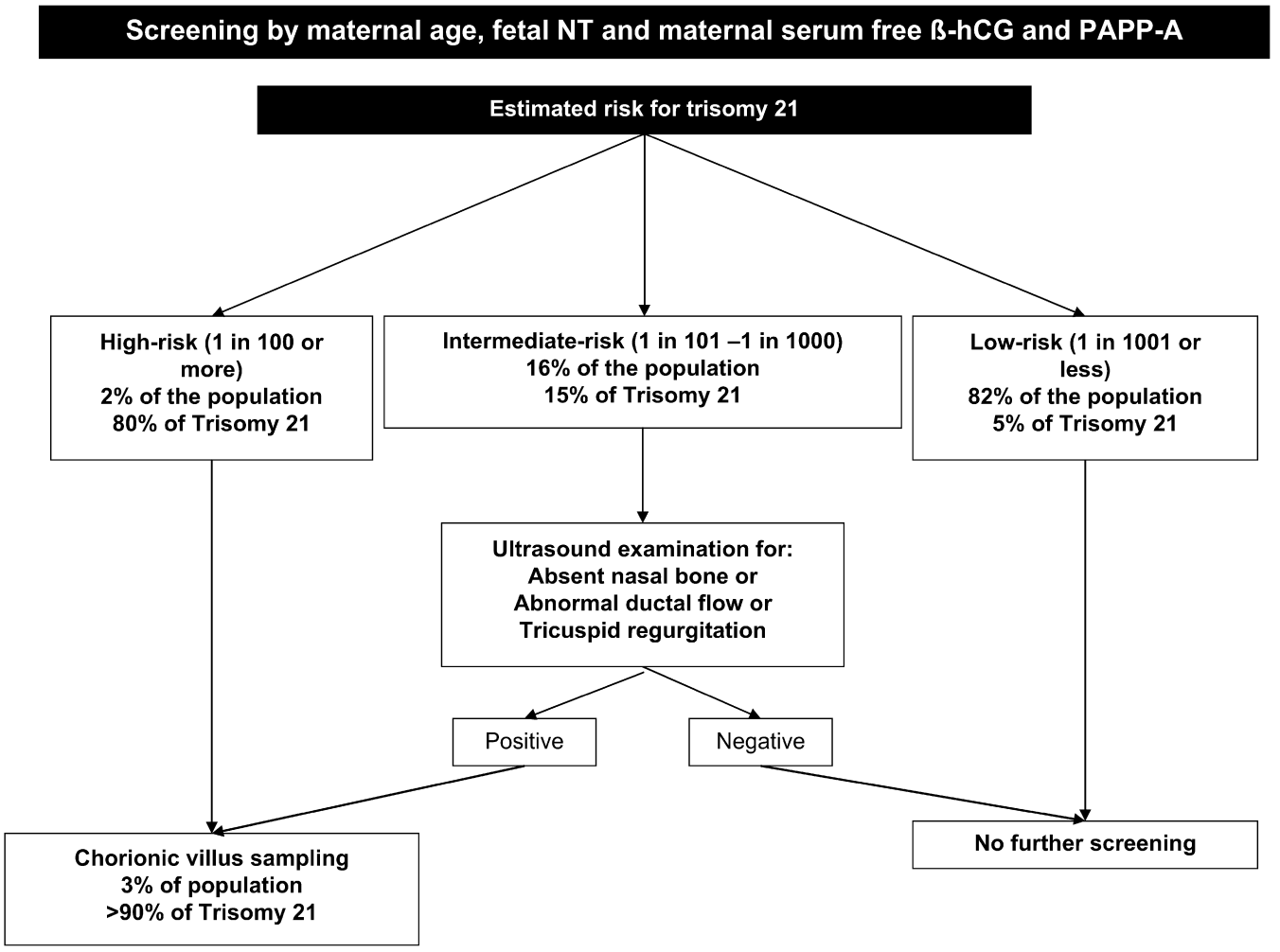

Figure 8 Two-tiered screening: first tier consists of the combination of NT measurement, β hCG, and PAPP-A; the second tier involves an evaluation of additional ultrasound markers such as the nasal bone, flow through the ductus venosus using Doppler, and tricuspid valve regurgitation also using Doppler. (Reprinted with modifications and permission from Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first trimester-screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. Ultrasound Obstet Gynecol 1998;2:380-4.

Kanellopulos et al[49] studied 501 fetuses and reported that nasal bone evaluation does not significantly prolong the time required for an ultrasound examination at 11 to 13^{+6} weeks' gestation.

Ideally, persons performing sonographic screening at 11 to 14 weeks' gestation should be versed both in NT measurement and nasal bone evaluation. However, because the experience needed for proficiency in nasal bone evaluation appears to be greater than for NT screening, an alternative approach was recently proposed by Nicolaides et al.[50] It is comprised of 2-tiered screening (Figure 8). The initial step involves routine screening using a NT measurement and maternal serum levels of free beta-hCG and PAPP-A. The patients are placed into 3 categories that are based on the results of the initial screening: a high-risk group (risk assessment of 1:100 or greater), intermediate-risk group (1:101-1,000), and low-risk group (1:1001 or less). The high-risk group is offered an invasive test (eg, a chorionic villus sampling [CVS]) and the low-risk group is reassured. The intermediate-risk is offered nasal bone evaluation or 1 of the other novel screening tests (ductus venosus Doppler[51] or tricuspid valve Doppler[52]) at a center specializing in these procedures. If the nasal bone is absent, the patient is offered an invasive procedure (eg, a CVS). If the nasal bone is present, the patient is reassigned into the low-risk category and reassured.

A recent prospective study in 21,074 singleton pregnancies with live fetuses at 11 to 13^{+6} weeks, incorporated assessment of the nasal bone into first-trimester combined screening by fetal NT thickness and maternal serum free ß-hCG and PAPP-A.[53]

Examination of the fetal nose was successful in 99% of the patients and the nasal bone was absent in 0.6% of the

Table X Prevalence of major and minor defects or markers in the second-trimester scan in trisomy 21 and chromosomally normal fetuses in the combined data of 2 major series*

	Trisomy 21	Normal	Positive LR	Negative LR	LR for isolated marker
Nuchal fold	107/319 (33.5%)	59/9331 (0.6%)	53.05 (39.37-71.26)	0.67 (0.61-0.72)	9.8
Short humerus	102/305 (33.4%)	136/9254 (1.5%)	22.76 (18.04-28.56)	0.68 (0.62-0.73)	4.1
Short femur	132/319 (41.4%)	486/9331 (5.2%)	7.94 (6.77-9.25)	0.62 (0.56-0.67)	1.6
Hydronephrosis	56/319 (17.6%)	242/9331 (2.6%)	6.77 (5.16-8.80)	0.85 (5.16-8.80)	1.0
Echogenic focus	75/266 (28.2%)	401/9119 (4.4%)	6.41 (5.15-7.90)	0.75 (0.69-0.80)	1.1
Echogenic bowel	39/293 (13.3%)	58/9227 (0.6%)	21.17 (14.34-31.06)	0.87 (0.83-0.91)	3.0
Major defect	75/350 (21.4%)	61/9384 (0.65%)	32.96 (23.90-43.28)	0.79 (0.74-0.83)	5.2

* From these data the positive and negative LRs (with 95% CI) for each marker can be calculated. In the last column is the LR for each marker found in isolation.[54-56]

chromosomally normal fetuses and in 62.1% of the 140 fetuses with trisomy 21. With combined screening, the detection rate of trisomy 21 was 90% for a false-positive rate of 5%. Inclusion of the nasal bone maintained the high detection rate at 90% with simultaneous halving in the false-positive rate to 2.5%. Furthermore, the study showed that examination of the nasal bone can either be carried out in all cases or in a subgroup of the population with an intermediate risk after the first stage of a 2-stage screening strategy. The choice between the 2 approaches, which have similar detection and false-positive rates, is dependent on the local availability of expertise in performing the nasal bone scan.

Second-trimester screening

Trisomy 21 and other major chromosomal defects are associated with sonographically detectable fetal anomalies and/or minor deviations from the normal (sonographic markers). Systematic examination of the fetus for anomalies and markers has led to the development of the so-called genetic sonogram. The findings on the genetic sonogram are used to adjust the a priori maternal age-related or serum biochemistry-related risk: the a priori risk of aneuploidy is multiplied by the likelihood ratios associated with the sonographic findings. The various likelihood ratios are derived by dividing the prevalence of a given defect or marker in chromosomally abnormal fetuses by its prevalence in chromosomally normal fetuses. The resultant likelihood ratio increases as the difference between the 2 prevalences increases, which leads to improvement of the screening test.

The genetic sonogram can be applied in essentially 2 situations. First, in women who are, either through advanced maternal age or second-trimester biochemical screening, considered to be at a sufficiently high risk for chromosomal defects to be offered an amniocentesis. A significant proportion of such women can be reassured by the absence of any sonographically detectable defects and they choose to not have an amniocentesis. Alternatively, the presence of markers and/or anomalies may increase their risk even further and may help them to make a decision in the opposite direction. Second, the genetic sonogram can also be used in low-risk women. In such cases, the presence of defects/markers will increase the risk of chromosomal defects. If the increase is sufficiently great to place the patient into the increased risk category, a discussion regarding an invasive test should take place.

Combined data from 2 large series that include a total of 350 fetuses with trisomy 21 and 9384 euploid fetuses, showed that fetal anomalies or a markers were detected in about 75% of affected fetuses and in about 13% of the chromosomally normal controls (Table X).[54-56] This table contains the individual likelihood ratios for commonly used markers and the overall likelihood ratio for major anomalies known to be associated with Down syndrome.

On the basis of current evidence, the prevalence of nasal bone absence in trisomy 21 fetuses in the second trimester is 37% and 1% in euploid fetuses, resulting in positive and negative likelihood ratios of 41 and 0.64, respectively (Table VI). As such, it appears to be a more important marker than most of the other sonographic features. Because examination of the fetal profile is an integral part of the genetic sonogram, assessment of the nasal bone will inevitably become a routine component of such a scan. The extent to which measurement of the NBL will also be incorporated into clinical practice remains to be determined. This will require further research into standardization of the measurement and establishment of accurate likelihood ratios, which take into account parental ethnicity, for each deviation in measurement from the normal median for gestation. However, at least 1 study[37] has shown that the inclusion of the nasal bone evaluation (both measurement and determination of presence vs absence) improves the performance of the traditional genetic sonogram.

Conclusion

The published data indicate that absence or hypoplasia of the nasal bone is strongly associated with trisomy 21: first, anthropomorphic studies have demonstrated that in postnatal life the nasal root depth is abnormally short in

about 50% of affected individuals; second, x-ray studies in aborted fetuses with trisomy reported that the prevalence of short or absent nasal bone in more than 60%; third, ultrasound studies in the first trimester have shown absence of the nasal bone in about 65% of trisomy 21 fetuses and in only 1% of normal fetuses; and fourth, ultrasound studies in the second trimester have shown absence or hypoplasia of the nasal bone in about 60% of trisomy 21 fetuses and in only 1% of normal fetuses.

The ethnic background, in both the first and second trimesters, affects the prevalence of nasal bone absence. NT measurement also appears to have an influence on the prevalence of nasal bone absence. Therefore, these factors need to be taken into account to generate accurate likelihood ratios associated with nasal bone presence and absence. Because nasal bone ossification does not start until approximately 11 weeks' gestation, using the nasal bone as a marker in trisomy 21 screening before that gestational age is not appropriate.

Both x-ray and 3D ultrasound data have demonstrated that unilateral nasal bone absence is not an uncommon finding in fetuses with trisomy 21. However, it appears to be very rare in the euploid population. The limited data available suggest that this does not have a significant effect on the efficacy of screening that uses 2D sonography.

The presence of a gap between the 2 developing nasal bones has now been documented by 3D ultrasound studies. It is present in approximately 20% of fetuses between 11 and 13^{+6} weeks' gestation, but the presence of the gap does not appear to be clinically significant.

The training and experience required to evaluate the nasal bone, especially in the first trimester, is considerable. However, this should not detract from using this technique in screening. It simply underscores the need for good training and quality control. After adequate training and using the appropriate technique, nasal bone evaluation improves the detection rate without significantly prolonging the time required for the ultrasound examination.

The manner in which nasal bone evaluation is used in general screening remains to be elucidated. Ideally, this technique will become as wide-spread as the NT measurement. Meanwhile, however, a 2-tiered screening strategy in which only those patients who fall into an intermediate-risk category are offered a nasal bone evaluation at a specialized center may be the best way to implement this technique.

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