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Nasal bone in first-trimester screening for trisomy 21

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KEY WORDS
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Objective: This study was undertaken to investigate the impact of incorporating assessment of the nasal bone into first-trimester combined screening by fetal nuchal translucency (NT) thickness and maternal serum biochemistry.

Study design: In this prospective combined screening study for trisomy 21, the fetal nasal bone was also examined and classified as present or absent. A multivariate approach was used to calculate patient-specific risks for trisomy 21 and the detection rate (DR) and false-positive rate (FPR) were estimated. We examined 2 screening strategies; first, integrated first-trimester screening in all patients and second, first-stage screening of all patients using fetal NT and maternal serum free ß-hCG and PAPP-A, followed by second-stage assessment of nasal bone only in those with an intermediate risk of 1 in 101 to 1 in 1000 after the first-stage.

Results: The nasal bone was absent in 113 (0.6%) of the 20,165 chromosomally or phenotypically normal fetuses and in 87 (62.1%) of the 140 fetuses with trisomy 21. With combined first-trimester NT and serum screening, the DR of 90% was achieved at a FPR of 5%. Inclusion of the nasal bone, either in all cases or in about 10% of the total in the 2-stage approach, halved the FPR to 2.5%.

Conclusion: Inclusion of the nasal bone in first-trimester combined screening for trisomy 21 achieves a DR of 90% for a FPR of 2.5%.

Trisomy 21, both in postnatal and in prenatal life, is associated with nasal hypoplasia. In 1866 Langdon Down noted that a common characteristic of patients with trisomy 21 is a small nose.[1] An anthropometric study in patients with trisomy 21 at age 7 months to 36 years reported that the nasal root depth is abnormally short in about 50% of cases.[2] In post mortem radiologic studies in fetuses with trisomy 21, aborted at 12 to 25 weeks, there was absence of ossification of the nasal bone or a very short nasal bone in about 65% of cases.[3] Ultrasound studies at 15 to 33 weeks of gestation, reported that the nasal bone is absent or very short in about 60% of fetuses with trisomy 21 and in 2% of normal fetuses.[3,4] Similarly, ultrasound studies at 11 to 13^{+6} weeks reported absence of the nasal bone in about 65% of fetuses with trisomy 21 and in 1% of chromosomally normal fetuses.[5-14] However, 1 study reported that the nasal bone was present in all 9 of their trisomy 21 fetuses.[15]

There is extensive evidence that effective screening for trisomy 21 and other major chromosomal abnormalities

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can be provided at 11 to 13^{+6} weeks of gestation by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum free-ß-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A). A prospective multicenter study, involving 75,821 singleton pregnancies undergoing first-trimester combined screening, demonstrated that, for a false-positive rate (FPR) of 5%, the detection rate of trisomy 21 was 90%.[16,17]

Case-control studies, comprising of 142 trisomy 21 and 7638 chromosomally normal pregnancies at 11 to 13^{+6} weeks, showed that there is no significant association between serum PAPP-A and free ß-hCG with absence of the nasal bone.[18,19] Consequently, examination of the nasal bone can be combined with maternal serum biochemistry and fetal NT thickness and such an integrated first-trimester sonographic and biochemical screening could improve the detection rate to more than 90% or reduce the FPR to less than 5%. However, the incidence of absent nasal bone decreases with fetal crown-rump length (CRL), increases with NT thickness and is substantially higher in Afro-Caribbean persons than in white persons,[7] and therefore, in the calculation of likelihood ratios in screening for trisomy 21 by nasal bone, adjustments must be made for these confounding factors.

There are essentially 2 possible ways in which examination of the nasal bone can be incorporated into first-trimester screening. First, the nasal bone can be examined in all cases and the likelihood ratio for presence or absence of a visible bone can be multiplied by the estimated risk from maternal age, fetal NT, and serum free ß-hCG and PAPP-A to derive a new integrated risk. Alternatively, because examination of the nasal bone can be difficult and requires extensive experience in first-trimester scanning,[20] this examination could be confined to a small subgroup of the patients.[16] It has been proposed that after combined fetal NT and maternal serum free ß-hCG and PAPP-A screening, patients are assigned a high-risk category with a risk estimate of 1 in 100 or more, a low-risk category with a risk estimate of less than 1 in 1000 and an intermediate-risk category with a risk estimate of between 1 in 101 and 1 in 1000.[16] Patients in the high-risk category would be offered karyotyping by chorionic villous sampling and those in the low-risk category would be reassured that their fetus is unlikely to be chromosomally abnormal. Those in the intermediate-risk category would have assessment of risk by first-trimester ultrasound examination for presence/absence of the nasal bone, and chorionic villous sampling would be offered if their adjusted risk is increased to become 1 in 100 or more.[16]

In this prospective study, involving more than 20,000 singleton pregnancies at 11 to 13^{+6} weeks, we investigate the potential impact of incorporating assessment of the nasal bone into first-trimester screening by fetal NT and maternal serum free ß-hCG and PAPP-A.

Methods

The fetal nasal bone was examined and classified as present or absent in women attending the Fetal Medicine Centre, London (between October 2001 and October 2004) for screening for trisomy 21 by a combination of fetal NT and maternal serum free ß-hCG and PAPP-A at 11 to 13^{+6} weeks.[16,21,22] The study was approved by the IRB of King's College Hospital and informed written consent was obtained from all women.

Serum free ß-hCG and PAPP-A were measured using the Kryptor analyser (Brahms AG, Berlin, Germany) and a transabdominal ultrasound examination was carried out to measure the fetal NT and to diagnose any major defects. The scans were carried out by 33 sonographers who had obtained the Fetal Medicine Foundation Certificate of competence in the 11 to 13^{+6} weeks scan and examination of the nasal bone (www.fetalmedicine.com). Each sonographer had at least 2 years of experience in obstetric ultrasound scanning and had carried out at least 500 NT scans before participating in this study.

For examination of the nasal bone, the image was magnified so that the head and the upper thorax only were included in the screen and a midsagittal view of the fetal profile was obtained.[5,20] The ultrasound transducer was parallel to the direction of the nose and the probe was gently tilted from one side to the other of the fetal nose. When these criteria were satisfied, 3 distinct lines were seen at the level of the fetal nose. The first 2, 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 continuity with the skin, but at a higher level, represents the tip of the nose. The nasal bone is considered to be present if it is more echogenic than the overlying skin and absent if it is either not visible or its echogenicity is the same or less than that of the skin.[5,20]

In our multidisciplinary 1-stop clinic for assessment of risk, 20 minutes were allocated for the scan and biochemical testing of the mother, ultrasound examination of the fetus and counselling were carried out within a 1-hour visit to the center. The patients were counselled with regard to their combined estimated risk and the available options for the subsequent management of the pregnancy, including chorionic villous sampling or amniocentesis. Data on pregnancy outcome were obtained from the cytogenetics laboratory, and by letters and telephone calls to the patients themselves, their general practitioners, or the maternity units in which they delivered.

Statistical analysis

Patient-specific risks for trisomy 21 were calculated by a multivariate approach. Essentially, the maternal age related risk was multiplied with each likelihood ratio (LR) derived from the fetal NT and maternal weight-adjusted serum free β-hCG and PAPP-A. The maximum and minimum LR allowed were 0.185 and 509 for NT, 0.014 and 62 for each free β-hCG and PAPP-A and 0.05 and 1000 for the combined sonographic and biochemical markers. In addition, we used the positive and negative LRs for trisomy 21 for absent and present nasal bone, respectively, to derive patient specific risks by a combination of maternal age, fetal NT and nasal bone, and maternal free ß-hCG and PAPP-A. The LRs used for present/absent nasal bone were as previously reported and take into account the interrelationship with maternal ethnic origin and fetal CRL and NT.[7]

Multiple logistic regression analysis was used to determine, in our study population, the significant contributors to absent nasal bone. In the analysis we examined maternal age in years, ethnic origin (white, Indian or Pakistani, Afro-Caribbean, Chinese or Japanese, mixed), maternal body mass index in kg/m^2, fetal karyotype (normal, trisomy 21, other chromosomal defect), fetal CRL in mm, and fetal NT as a deviation in mm from the normal mean for CRL.[21] Similarly, multiple logistic regression analysis was used to determine the significant contributors to the inability to evaluate the nasal bone.

We calculated the detection rates of trisomy 21 for fixed FPRs between 1% and 10% and the FPRs for fixed detection rates between 65% and 95% by maternal age alone, maternal age and fetal NT, maternal age and serum free ß-hCG and PAPP-A, by a combination of maternal age, fetal NT, and maternal serum biochemistry and by a combination of maternal age, fetal NT, and nasal bone and maternal serum biochemistry. In terms of the nasal bone, we examined 2 screening strategies: first, assessment of the nasal bone in all patients and second, first-stage screening of all patients using fetal NT and maternal serum free ß-hCG and PAPP-A, followed by second-stage assessment of nasal bone only in those with an intermediate-risk after the first-stage.[16] We examined the performance of 2-stage screening, in terms of percentage of the population requiring assessment of the nasal bone and overall detection rate (DR) and FPR, using different estimated risks to define the intermediate-risk category. We also examined the performance of screening in the general population. First, we generated a database of 20,305 cases with the maternal age distribution of live births in England and Wales in 2003, which is similar to that in the United States in the same year, and ordered this in increasing maternal age.[23,24] Second, we used the database containing the ultrasound and biochemical findings of our cases with normal karyotype (n = 20,165) and those with trisomy 21 (n = 140) and ordered the cases by maternal age and hospital identification number. Third, we merged the 2 databases, replaced the true maternal age of each of our cases with that from the database of the general population and recalculated patient-specific risks for trisomy 21, as described in the first paragraph of statistical analysis above.

Table I Prevalence of absent nasal bone in chromosomally normal and abnormal fetuses at 11 to 13^{+6} weeks

Fetal karyotype	N	Absent nasal bone
Normal	20,165	113 (0.6%)
Trisomy 21	140	87 (62.1%)
Trisomy 18	40	22 (55.0%)
Trisomy 13	19	6 (31.6%)
Turner syndrome	13	5 (38.5%)
Triploidy	11	1 (9.1%)
Other*	30	4 (13.3%)
Total	20,418	238 (1.2%)

* Trisomies or sex chromosome aneuploidies other than above, unbalanced translocations, deletions, mosaics.

Results

Screening for trisomy 21 was carried out in 21,074 singleton pregnancies with live fetuses at 11 to 13^{+6} (median 12) weeks. Fetal NT and maternal serum free ß-hCG and PAPP-A were successfully measured in all cases. Pregnancy outcome, including karyotype results or the birth of a phenotypically normal infant, was obtained from 20,418 (96.9%) cases. Excluded from further analysis were 656 cases, because the fetal karyotype was not known and they resulted in spontaneous fetal loss (n = 185) or termination of pregnancy (n = 85) or were lost to follow-up (n = 386).

In the 20,418 cases included in the analysis, the median maternal age was 35 (range 18-50) years, the median fetal CRL was 62 (range 45-84) mm, and the ethnic origin of the women was white in 19,209 (94.0%), Indian or Pakistani in 790 (3.9%), Afro-Caribbean in 174 (0.9%), Chinese or Japanese in 164 (0.8%), and mixed in 81 (0.4%). Chromosomal abnormalities were identified in 253 pregnancies, including 140 cases of trisomy 21 (Table I). In the total group, the fetal nasal bone was recorded as absent in 238 (1.2%) cases, present in 19,937 (97.6%), and as unable to examine in 243 (1.2%). The respective values in the 140 fetuses with trisomy 21 were 87 (62.1%), 52 (37.2%), and 1 (0.7%).

Multiple logistic regression analysis demonstrated that the significant contributors to absent nasal bone were trisomy 21 (odds ratio [OR] = 127.2, 95% CI 78.5-206.0, $P < .0001$), other chromosomal defects (OR = 17.4, 95% CI 9.4-32.3, $P < .0001$), Afro-Caribbean

Table II Detection rates for different FPRs in screening for trisomy 21, by maternal age, fetal NT, maternal serum free ß-hCG and PAPP-A and fetal nasal bone either in all patients or in those with combined risk of 1 in 51 to 1 in 1,000 (in our population there were 20,165 normal and 140 trisomy 21 pregnancies)

	DRs for different FPRs									
Method of screening	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	10%
MA	8.6%	11.4%	14.3%	16.4%	19.3%	20.0%	20.7%	22.2%	24.3%	37.2%
MA and NT	62.2%	65%	65.7%	69.3%	72.2%	73.6%	75.0%	77.1%	81.4%	89.3%
MA and ß-hCG and PAPP-A	32.1%	41.4%	44.3%	49.3%	52.8%	57.8%	58.6%	62.8%	66.4%	78.6%
MA and NT and ß-hCG and PAPP-A	75.7%	77.8%	78.6%	82.1%	85.7%	87.1%	87.8%	88.6%	90.0%	95.0%
MA, NT, ß-hCG, PAPP-A and NB in all cases	87.1%	87.8%	87.8%	90.0%	91.4%	92.8%	93.6%	93.6%	93.6%	96.4%
MA, NT, ß-hCG and PAPP-A in all and NB in those with risk of 1 in 51 to 1 in 1,000	85.0%	87.9%	87.9%	90.0%	92.1%	92.9%	93.6%	93.6%	93.6%	96.4%

MA, Maternal age; *NB,* nasal bone.

Table III FPRs for different DRs in screening for trisomy 21 by maternal age, fetal NT thickness, maternal serum free ß-hCG and PAPP-A and fetal nasal bone either in all patients or in those with combined risk of 1 in 51 to 1 in 1,000 (in our population there were 20,165 normal and 140 trisomy 21 pregnancies)

	FPRs for different DRs						
Method of screening	65%	70%	75%	80%	85%	90%	95%
MA	30.0%	37.0%	39.8%	46.5%	55.7%	63.8%	76.9%
MA and NT	1.5%	2.5%	3.9%	4.9%	7.1%	12.1%	29.9%
MA and ß-hCG and PAPP-A	4.7%	5.6%	8.4%	11.2%	16.2%	20.7%	35.2%
MA, NT and ß-hCG and PAPP-A	0.3%	0.5%	0.8%	2.2%	2.8%	4.8%	9.0%
MA, NT, ß-hCG, PAPP-A and NB in all cases	0.2%	0.2%	0.4%	0.5%	0.7%	2.5%	6.7%
MA, NT, ß-hCG and PAPP-A in all and NB in those with risk of 1 in 51 to 1 in 1,000	0.3%	0.3%	0.5%	0.6%	1.0%	2.4%	6.4%

ethnic origin (OR = 5.6, 95% CI 2.2-14.2, $P < .0001$), deviation in fetal NT from the normal mean for CRL (OR = 1.6, 95% CI 1.4-1.8, $P < .0001$), fetal CRL (OR = 0.94, 95% CI 0.92-0.96, $P < .0001$), and maternal age (OR = 1.07, 95% CI 1.03-1.11, $P = .002$). There was no significant contribution from maternal body mass index. In contrast, the only significant contributor to the inability to evaluate the nasal bone was the maternal body mass index (OR = 1.05, 95% CI 1.04-1.06, $P < .0001$).

The DRs of trisomy 21 for fixed FPRs between 1% and 10% and the FPRs for fixed DRs between 65% and 95% by maternal age alone, maternal age and fetal NT, maternal age and serum free ß-hCG and PAPP-A, by a combination of maternal age, fetal NT, and maternal serum biochemistry and by a combination of maternal age, fetal NT, and nasal bone and maternal serum biochemistry are shown in Tables II and III, respectively. With combined first-trimester NT and serum screening, the DR of 90% was achieved at a FPR of 5%. Inclusion of the nasal bone, either in all cases or in the 2-stage approach, reduced the FPR to about 2.5%, without decreasing the 90% DR.

The performance of 2-stage screening, in terms of percentage of the population requiring assessment of the nasal bone and overall DR of trisomy 21 and FPR, in our study group is shown in Table IV and in a population standardized to the maternal age distribution of live births in England and Wales[23] is shown in Table V. For example, in our study group with median maternal age of 35 years, if the estimated risk of 1 in 51 to 1 in 150 is used, only 2.4% of the patients would require assessment of the nasal bone and the overall DR of trisomy 21 would be 85%, whereas, if the estimated risk of 1 in 51 to 1 in 1000 is used, 15.3% of the population would require assessment of the nasal bone and the overall DR of trisomy 21 would be 90.7% (Table IV). In the general population, with median maternal age of 29 years,[23] if the high-risk group is defined by an estimated risk of 1 in 100 or more and the intermediate-risk group is defined by a risk of 1 in 101 to 1 in 1000, 8.3% of the patients would require assessment of the nasal bone and the overall FPRs and DRs would be 2.2% and 89.3%, respectively (Table V).

Comment

The findings of this prospective study confirm the high association between absent nasal bone at the 11 to 13^{+6} weeks scan and trisomy 21, as well as other major chromosomal defects. Furthermore, the data demonstrate that examination of the nasal bone can be combined

Table IV Performance of 2-stage screening, in terms of percentage of the population requiring assessment of the nasal bone and overall DR of trisomy 21 and FPR, using different estimated risks to define the intermediate-risk category (in our population there were 20,165 normal and 140 trisomy 21 pregnancies)

Intermediate-risk group	NB scan (n = 20,305)	FPR (n = 20,165)	DR (n = 140)
1 in 51 to 1 in 100	282 (1.4%)	454 (2.25%)	117 (83.6%)
1 in 51 to 1 in 150	496 (2.4%)	458 (2.27%)	119 (85.0%)
1 in 51 to 1 in 200	719 (3.5%)	462 (2.29%)	123 (87.9%)
1 in 51 to 1 in 500	1,682 (8.3%)	471 (2.34%)	125 (89.3%)
1 in 51 to 1 in 1,000	3,113 (15.3%)	480 (2.38%)	127 (90.7%)

The median maternal age was 35 y.

Table V Estimated performance of 2-stage screening in a population with the maternal age distribution of live births in England and Wales in 2003

Intermediate-risk group	NB scan	FPR	DR
High risk 1 in 25		0.52%	70.7%
1 in 26 to 1 in 250	3.4%	0.61%	80.0%
1 in 26 to 1 in 500	5.9%	0.66%	84.3%
1 in 26 to 1 in 1,000	9.9%	0.67%	85.0%
1 in 26 to 1 in 1,500	13.4%	0.67%	85.0%
High risk 1 in 50		1.07%	77.9%
1 in 51 to 1 in 250	2.8%	1.15%	82.1%
1 in 51 to 1 in 500	5.3%	1.20%	86.4%
1 in 51 to 1 in 1,000	9.3%	1.22%	87.1%
1 in 51 to 1 in 1,500	12.8%	1.23%	87.9%
High risk 1 in 100		2.06%	80.7%
1 in 101 to 1 in 250	1.8%	2.11%	84.3%
1 in 101 to 1 in 500	4.3%	2.16%	88.6%
1 in 101 to 1 in 1,000	8.3%	2.20%	89.3%
1 in 101 to 1 in 1,500	11.8%	2.22%	90.0%
High risk 1 in 150		2.76%	82.1%
1 in 151 to 1 in 250	1.1%	2.78%	84.3%
1 in 151 to 1 in 500	3.6%	2.83%	88.6%
1 in 151 to 1 in 1,000	7.6%	2.87%	89.3%
1 in 151 to 1 in 1,500	11.1%	2.89%	90.0%

The median maternal age was 29 y. The first column defines the high-risk and intermediate-risk groups, in the second column is the percentage of the population requiring assessment of the NB, in the third column is the overall DR of trisomy 21 and in the fourth column is the FPR.

with maternal serum biochemistry and fetal NT thickness in first-trimester screening for trisomy 21 to achieve a detection rate of 90%, with a halving in the FPR from about 5% to 2.5%.

The main contributors to the finding of absent nasal bone in our population were the presence of trisomy 21, other chromosomal defects, Afro-Caribbean ethnic origin, high fetal NT, and low CRL, with a small contribution from maternal age. The only contributor to the inability to assess the nasal bone was increased body mass index. Examination of the fetal nose was successful in about 99% of the patients and in our predominantly white population there was absence of the nasal bone in about 60% of the trisomy 21 fetuses and in 0.6% of the chromosomally normal fetuses. These results, which are compatible with those from specialist centere,[7-14] were achieved by sonographers with extensive training and experience in the 11 to 13^{+6} weeks scan.[20] The importance of such expertise and the adherence to standardized techniques are highlighted by the findings of a multicenter study, which included examination of the nasal bone in 6324 cases.[15] In this study, in which a midsagittal plane of the fetus was obtained in only 50% of the cases,[25] successful examination of the nasal bone was achieved in only 76% of the cases and the nasal bone was apparently present in all 9 fetuses with trisomy 21.[15] We have shown that the minimum number of scans required for an experienced sonographer to become competent in examining the fetal nasal bone is 120 and that it is imperative that sonographers undertaking risk assessment by examination of the fetal profile receive appropriate training and certification of their competence in performing such a scan.[20]

In the evaluation of the performance of different screening strategies it is important to either compare the DR for fixed FPRs (Table II) or alternatively to compare the FPR for fixed DRs (Table III). The traditionally acceptable FPR in screening for trisomy 21 is about 5%. As demonstrated by many previous studies and confirmed by the findings of the present one, at a 5% FPR, the DR of trisomy 21 is about 25% in screening by maternal age alone, and this increases to about 80% when fetal NT is included and 90% when maternal serum free ß-hCG and PAPP-A are also used. Inclusion of assessment of the nasal bone in first-trimester screening improves the detection rate further to about 95%. Alternatively, it could be argued that with improved screening, more emphasis should now be placed in reducing the FPR and the consequent human cost, in terms of fetal death and miscarriage, as well as the economic cost from invasive diagnostic testing. As demonstrated by our findings, a high DR of 90% with simultaneous halving in the FPR to 2.5%, can now be achieved by inclusion of assessment of the nasal bone in the first-trimester strategy of combined sonographic and biochemical screening.

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 DRs and FPRs, is dependent on the local availability of expertise in performing the nasal bone scan. Ideally, in screening all the necessary information from the sonographic examination and biochemical testing should be available in the same patient visit so that counselling can be undertaken with the provision of a single combined risk estimate.[26] We have previously shown that, once such an estimate is given, the women are capable of making a rational decision in favor or against invasive diagnostic testing.[27] In the 2-stage approach, assessment of risk is firstly carried out by fetal NT and maternal serum free ß-hCG and PAPP-A and nasal bone examination is then carried out only in those with a risk estimate of between 1 in 101 and 1 in 1000, which constitutes about 10% of the total. If the expertise for examination of the nasal bone is not available in the primary screening center, the patients in the intermediate-risk category could be referred to a more specialist unit to undergo such examination and readjustment of risk.

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