

# Fetal nasal bone in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation

K. O. KAGAN\*†, S. CICERO\*, I. STABOULIDOU\*, D. WRIGHT‡ and K. H. NICOLAIDES\*

\*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London and †Department of Mathematics and Statistics, University of Plymouth, Plymouth, UK and ‡Department of Obstetrics and Gynaecology, University of Tuebingen, Tuebingen, Germany

**KEYWORDS:** free  $\beta$ -hCG; first-trimester screening; nasal bone; nuchal translucency; PAPP-A; trisomy 21

## ABSTRACT

**Objective** To investigate the performance of first-trimester screening for aneuploidies by including assessment of the fetal nasal bone in the combined test of maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate (FHR) and serum free  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) and pregnancy-associated plasma protein-A (PAPP-A).

**Methods** Screening by the combined test was performed in singleton pregnancies, including 19 614 with euploid fetuses, 122 with trisomy 21, 36 with trisomy 18, 20 with trisomy 13 and eight with Turner syndrome. In all cases the fetal nasal bone was assessed and classified as present or absent. We examined the performance of two screening strategies: firstly, assessment of the nasal bone in all patients and secondly, first-stage screening using the combined test in all patients followed by second-stage assessment of the nasal bone only in those with an intermediate risk of 1 in 51 to 1 in 1000 after the first stage. To validate the new risk algorithm we used a second independent dataset of 19 651 fetuses, including 139 with trisomy 21.

**Results** The nasal bone was absent in 2.6% of the euploid fetuses, 59.8% with trisomy 21, 52.8% with trisomy 18, 45.0% with trisomy 13 and in none of the fetuses with Turner syndrome. Respective figures for an absent nasal bone in the validation population, which contained fewer Black women, were 0.6%, 62.6%, 55.3%, 35.3% and 41.7%. In a screening policy based on maternal age, fetal NT, FHR, serum free  $\beta$ -hCG and PAPP-A, for a fixed risk cut-off of 1:100, the false-positive rate was 3.0%. The standardized detection rates were 91% for trisomy 21 and 100% for trisomy 18, trisomy 13 and Turner syndrome, respectively. Assessment of the nasal bone in all pregnancies reduced the false-positive rate to 2.5%

without changing the detection rate. A detection rate of 93% was achieved with the two-stage strategy at a false-positive rate of 2.4% in which it was necessary to assess the nasal bone in only 15% of the total population. In the validation dataset, screening by the combined test and using a risk cut-off of 1:100 detected 90% of the cases with trisomy 21 for a false-positive rate of 4%. Inclusion of the nasal bone increased the detection rate to 92% for a false-positive rate of 2.9%. Contingent screening detected 92% of cases for a false-positive rate of 2.9%.

**Conclusions** Assessment of the fetal nasal bone improves the performance of first-trimester screening for trisomy 21. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.

## INTRODUCTION

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<sup>1</sup>. In the combined data from four postmortem radiologic 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% of cases and nasal hypoplasia in 21.4% of cases<sup>2–5</sup>. Sonographic studies at 11–24 weeks of gestation reported that approximately 65% of trisomy 21 fetuses have absent or short nasal bone<sup>6–11</sup>.

We have recently reported the development of specific algorithms for first-trimester screening for trisomy 21, trisomy 18 and trisomy 13, based on maternal age, fetal nuchal translucency (NT), fetal heart rate (FHR) and maternal serum free  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) and pregnancy-associated plasma protein-A (PAPP-A) (combined test)<sup>12,13</sup>. When all three algorithms

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK (e-mail: fmf@fetalmedicine.com)

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are used the estimated detection rates of trisomies 21, 18 and 13 are 91%, 97%, and 94%, respectively, for an overall false-positive rate of 3.1%<sup>13</sup>.

The aims of this study were to derive a specific algorithm that incorporates assessment of the nasal bone into the combined first-trimester screening test and to examine the performance of such an algorithm in screening for trisomies 21, 18 and 13 and Turner syndrome. We examined the performance of two screening strategies: firstly, assessment of the nasal bone in all patients and secondly, first-stage screening using the combined test followed by second-stage assessment of the nasal bone only in those with an intermediate risk for trisomies 21, 18 and 13 and Turner syndrome of between 1 in 51 and 1 in 1000.

## METHODS

This was a prospective screening study for trisomy 21 in singleton pregnancies by a combination of maternal age, fetal NT thickness and maternal serum free  $\beta$ -hCG and PAPP-A in a one-stop clinic for first-trimester assessment of risk (OSCAR) at 11 + 0 to 13 + 6 weeks of gestation<sup>14,15</sup>. Transabdominal ultrasound examination was performed to diagnose any major fetal defects and for measurement of fetal crown-rump length (CRL), NT thickness and FHR. Assessment of the nasal bone was also routinely performed by sonographers who had received the appropriate Fetal Medicine Foundation Certificates of Competence. Automated machines that provide reproducible results within 30 min were used to measure PAPP-A and free  $\beta$ -hCG (Delfia Express System, Perkin Elmer, Waltham, MA, USA).

Maternal demographic characteristics, ultrasonographic measurements and biochemical results were recorded in a computer database. Karyotype results and details on pregnancy outcomes were added into the database as soon as they became available. A search of the database was done to identify all singleton pregnancies in which first-trimester combined screening was carried out from January 2006 to May 2007.

The fetal nasal bone was examined and classified as present or absent<sup>6,16</sup>. For examination of the nasal bone, the image was magnified so that the head and the upper thorax only were included on the screen and a mid-sagittal view of the fetal profile was obtained. The ultrasound transducer was placed 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, three distinct lines were seen at the level of the fetal nose. The first two, which are proximal to the forehead, are horizontal and parallel to each other, resembling an 'equals sign'. The top line represents the skin and the bottom one, 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 either it is not visible or its echogenicity is the same or less than that of the skin.

To validate the new risk algorithm based on combined screening with the addition of assessment of the nasal bone we used a second independent dataset with about 20 000 euploid fetuses and 139 cases with trisomy 21. This dataset was derived from our previous nasal bone screening study from 2001 to 2004<sup>11</sup>.

## Statistical analysis

Firstly, we estimated the risk for trisomy 21, trisomy 18, trisomy 13 and Turner syndrome by the combined test based on maternal age, fetal NT, FHR, free  $\beta$ -hCG and PAPP-A<sup>13</sup>. Secondly, this risk was modified by the findings from assessment of the nasal bone. In order to do this we used multiple logistic regression to model the conditional probability of absent nasal bone given fetal karyotype, fetal NT, free  $\beta$ -hCG and PAPP-A and covariates representing ethnicity and maternal smoking status. Thirdly, Bayes' theorem was applied to produce risks of trisomy 21, trisomy 18, trisomy 13 and Turner syndrome.

We examined the performance of two screening strategies: firstly, assessment of the nasal bone in all patients and secondly, first-stage screening using the combined test followed by second-stage assessment of the nasal bone in only those with an intermediate risk for trisomies 21, 18 and 13 and Turner syndrome of between 1 in 51 and 1 in 1000.

Screening performance was assessed by calculating the proportions with risks above a given risk threshold after adjustment for maternal age according to the distribution of pregnancies in England and Wales in 2000–2002 (Office for National Statistics, 2000–2002)<sup>17</sup>.

## RESULTS

### Study population (development dataset)

The search of the database identified 21 141 singleton pregnancies. In 1110 (5.3%) cases the outcome was not available, in 188 (0.9%) cases one of the covariates was missing, including 52 (0.25%) cases where it was not possible to assess the nasal bone properly. In 43 (0.20%) cases there was a chromosomal abnormality other than trisomies 21, 18 or 13 or Turner syndrome. Thus, our study population consisted of 19 614 pregnancies with a normal karyotype or delivery of a phenotypically normal baby (euploid group), 122 cases of trisomy 21, 36 cases of trisomy 18, 20 cases of trisomy 13 and eight cases of Turner syndrome. The characteristics of the study population are summarized in Table 1.

### Fetal NT, FHR and maternal serum biochemistry

The distributions of fetal CRL, NT, FHR and maternal serum free  $\beta$ -hCG and PAPP-A in fetuses with trisomies 21, 18 and 13 and Turner syndrome are shown in Table 2.

Table 1 Study characteristics

Characteristic	Study population	Validation population
Maternal characteristics		
Age (years, median (range))	34.5 (14.1–50.1)	35.2 (18.1–50.5)
Weight (kg, median (range))	64.0 (34.0–165.0)	63.0 (35.4–150.0)
Spontaneous conception ( <i>n</i> (%))	19 038 (96.2)	18 806 (95.7)
Smoker ( <i>n</i> (%))	1145 (5.8)	645 (3.3)
Ethnicity ( <i>n</i> (%))		
Caucasian	15 850 (80.1)	18 479 (94.0)
Afro-Caribbean	2148 (10.8)	170 (0.9)
East Asian	271 (1.4)	163 (0.8)
South Asian	1031 (5.2)	760 (3.9)
Mixed	500 (2.5)	79 (0.4)
Gestational age		
11 + 0 to 11 + 6 weeks ( <i>n</i> (%))	1477 (7.5)	2313 (11.8)
12 + 0 to 12 + 6 weeks ( <i>n</i> (%))	11 495 (58.0)	11 612 (59.1)
13 + 0 to 13 + 6 weeks ( <i>n</i> (%))	6828 (34.5)	5726 (29.1)
CRL (mm, median (range))	63 (45.0–84.0)	61.9 (45.0–84.0)
Karyotype ( <i>n</i> (%))		
Euploid	19 614 (99.06)	19 445 (98.95)
Trisomy 21	122 (0.62)	139 (0.71)
Trisomy 18	36 (0.18)	38 (0.19)
Trisomy 13	20 (0.10)	17 (0.09)
Turner syndrome	8 (0.04)	12 (0.06)
Total	19 800 (100.0)	19 651 (100.0)

CRL, crown–rump length.

Table 2 Fetal crown–rump length, nuchal translucency thickness (NT), heart rate, serum pregnancy-associated plasma protein-A (PAPP-A) and serum free  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) in chromosomally normal and abnormal fetuses

Characteristic	Study population	Validation population
Crown–rump length (mm, median (range))		
Euploid	63.2 (45.0–84.0)	61.9 (45.0–84.0)
Trisomy 21	63.1 (47.4–84.0)	62.5 (47.3–84.0)
Trisomy 18	55.1 (45.0–70.4)	51.0 (45.0–84.0)
Trisomy 13	57.0 (45.5–82.9)	59.8 (47.9–73.2)
Turner syndrome	62.0 (45.0–69.7)	60.4 (51.7–70.7)
Observed deviation from expected fetal NT (mm, median (range))		
Euploid	0.1 (–1.0 to 8.5)	0 (–1.1 to 10.4)
Trisomy 21	1.4 (–0.4 to 11.2)	1.8 (–0.3 to 9.7)
Trisomy 18	2.6 (–0.4 to 9.3)	3.0 (–0.6 to 12.0)
Trisomy 13	3.1 (0.0–6.3)	1.9 (–0.4 to 5.7)
Turner syndrome	8.5 (1.5–10.4)	7.6 (–0.1 to 16.5)
PAPP-A (MoM, median (range))		
Euploid	1.0 (0.2–3.3)	1.0 (0.1–8.4)
Trisomy 21	0.5 (0.06–2.2)	0.5 (0.1–1.9)
Trisomy 18	0.2 (0.03–3.9)	0.2 (0.04–1.5)
Trisomy 13	0.3 (0.1–0.6)	0.3 (0.1–1.0)
Turner syndrome	0.5 (0.3–0.8)	0.4 (0.1–1.3)
Free $\beta$ -hCG (MoM, median (range))		
Euploid	1.0 (0.1–29.4)	1.0 (0.1–12.0)
Trisomy 21	2.0 (0.1–7.0)	1.8 (0.4–7.5)
Trisomy 18	0.2 (0.02–4.8)	0.3 (0.06–2.3)
Trisomy 13	0.4 (0.2–1.1)	0.6 (0.2–3.4)
Turner syndrome	1.2 (0.3–2.0)	1.0 (0.3–2.6)
Observed deviation from expected fetal heart rate (bpm, median (range))		
Euploid	–0.1 (–32.4 to 45.4)	–0.3 (–34.2 to 26.9)
Trisomy 21	0.6 (–21.6 to 17.8)	1.5 (–27.1 to 31.2)
Trisomy 18	–3.4 (–17.4 to 10.5)	–1.3 (–19.5 to 20.0)
Trisomy 13	18.4 (10.5–32.0)	16.2 (–11.7 to 38.0)
Turner syndrome	2.1 (–3.9 to 9.5)	8.5 (–17.4 to 26.0)

bpm, beats per minute; MoM, multiples of the median.

## Nasal bone

In the development dataset the nasal bone was absent in 2.6% of the euploid fetuses, in 59.8% with trisomy 21, 52.8% with trisomy 18, 45.0% with trisomy 13 and in none of the fetuses with Turner syndrome. Respective figures for an absent nasal bone in the validation dataset were 0.6%, 62.6%, 55.3%, 35.3% and 41.7% (Table 3).

Logistic regression analysis in the development dataset demonstrated significant effects on the prevalence of an

**Table 3** Prevalence of absent nasal bone in chromosomally normal and abnormal pregnancies in the study population and in the validation dataset

Karyotype	Study population		Validation population	
	n	Absent nasal bone (n (%))	n	Absent nasal bone (n (%))
Euploid	19 614	513 (2.6)	19445	109 (0.6)
Trisomy 21	122	73 (59.8)	139	87 (62.6)
Trisomy 18	36	19 (52.8)	38	21 (55.3)
Trisomy 13	20	9 (45.0)	17	6 (35.3)
Turner syndrome	8	0 (0)	12	5 (41.7)
Total	19 800	614 (3.1)	19 651	228 (1.2)

absent nasal bone from Afro-Caribbean ethnicity, fetal NT, fetal CRL, serum PAPP-A, free  $\beta$ -hCG, smoking status and fetal karyotype (Table 4).

## Risk distribution and test performance

The performance of screening is shown in Tables 5 and 6. In screening by maternal age, fetal NT, FHR, serum free  $\beta$ -hCG and PAPP-A with a fixed risk cut-off of 1:100, for the total risk for trisomies 21, 18, 13 and Turner syndrome, the standardized false-positive rate was 3.0% and the respective detection rates for trisomies 21, 18 and 13 and Turner syndrome were 91%, 100%, 100% and 100% (Table 5). Assessment of the nasal bone in all pregnancies would lead to a further decrease in the false-positive rate by 17% to 2.5% without decreasing the detection rate. In the validation dataset, for the same risk cut-off of 1:100, in screening by maternal age, fetal NT, FHR, serum free  $\beta$ -hCG and PAPP-A the false-positive rate would be 4.0% and the detection rate of trisomy 21 would be 90%. Inclusion of the nasal bone would be associated with a 28% decrease in the false-positive rate to 2.9% and a small increase in the detection rate to 92%.

The total risk for trisomies 21, 18, 13 and Turner syndrome, according to maternal age, fetal NT, FHR,

**Table 4** Fitted logistic regression model for the probability of an absent nasal bone

Parameter	Coefficient	Standard error	z	P	Odds ratio (95% CI)
Constant	1.41525	0.38131	3.712	0.0002	
Smoker/non-smoker	0.40028	0.16578	2.415	0.0158	1.492 (1.078–2.065)
Nuchal translucency (mm)	0.33977	0.05432	6.255	<0.0001	1.405 (1.263–1.562)
Crown–rump length (mm)	–0.09583	0.00648	–14.8	<0.0001	0.909 (0.897–0.920)
log MoM PAPP-A	–0.43101	0.18230	–2.36	0.0181	0.650 (0.455–0.929)
log MoM $\beta$ -hCG	0.36029	0.16798	2.145	0.0320	1.434 (1.032–1.993)
Trisomy 21/euploid	3.60897	0.24130	14.96	<0.0001	36.928 (23.012–59.259)
Trisomy 13/euploid	2.15925	0.52310	4.128	<0.0001	8.665 (3.108–24.156)
Trisomy 18/euploid	2.31695	0.44024	5.263	<0.0001	10.145 (4.281–24.042)
Afro-Caribbean/White	1.21343	0.10800	11.24	<0.0001	3.365 (2.723–4.158)
Asian/White	0.29148	0.19781	1.473	0.1406	1.338 (0.908–1.972)
Mixed ethnicity/White	0.47026	0.26186	1.796	0.0725	1.600 (0.958–2.674)
Oriental/White	0.20374	0.39964	0.51	0.6102	1.226 (0.560–2.683)

$\beta$ -hCG,  $\beta$ -human chorionic gonadotropin; MoM, multiples of the median; PAPP-A, pregnancy-associated plasma protein-A.

**Table 5** Detection and false-positive rates for given risk cut-offs in screening by the total risk for trisomy 21, 18, 13 and Turner syndrome based on maternal age, fetal nuchal translucency, fetal heart rate, maternal serum free  $\beta$ -human chorionic gonadotropin and pregnancy-associated plasma protein-A without and with assessment of the nasal bone (X/Y in each cell) in the development and the validation datasets

Risk cut-off	False-positive rate (%)		Detection rate (%)							
			Trisomy 21		Trisomy 18		Trisomy 13		Turner syndrome	
Development (n = 19 614)	Validation (n = 19 445)	Development (n = 122)	Validation (n = 139)	Development (n = 36)	Validation (n = 38)	Development (n = 20)	Validation (n = 17)	Development (n = 8)	Validation (n = 12)	
1:50	1.6/1.4	2.3/1.8	85/90	89/90	88/87	93/93	100/100	83/83	100/100	95/95
1:100	3.0/2.5	4.0/2.9	91/91	90/92	100/92	97/93	100/100	89/83	100/100	95/95
1:200	5.2/4.3	6.0/4.4	94/95	93/94	100/92	97/97	100/100	100/100	100/100	95/95
1:300	6.9/5.8	8.2/5.8	95/95	94/94	100/92	97/97	100/100	100/100	100/100	95/95

All rates standardized to the maternal age distribution of pregnancies in England and Wales in 2000–2002<sup>17</sup>.

Table 6 Distribution of risk and effectiveness of contingent screening in development and validation datasets

Fetal karyotype	Risk estimated from first-stage screening			Risk estimated from second-stage screening	Total false-positive and detection rate (%)
	≥ 1 in 50 (%)	1 in 51 to 1 in 1000 (%)	< 1 in 1000 (%)	> 1 in 100 (%)	
Development dataset					
Euploid	1.6	14.6	83.8	0.8	2.4
Trisomy 21	85.4	13.4	1.2	7.4	92.8
Trisomy 18	88.4	11.6	0.0	3.4	91.8
Trisomy 13	100	0.0	0.0	0.0	100
Turner syndrome	100	0.0	0.0	0.0	100
Validation dataset					
Euploid	2.3	17.5	80.2	0.6	2.9
Trisomy 21	88.5	9.7	1.8	3.2	91.7
Trisomy 18	93.4	3.3	3.3	0.0	93.4
Trisomy 13	83.1	16.9	0.0	0.0	83.1
Turner syndrome	95.0	5.0	0.0	0.0	95.0

In the first stage the patients are divided into three risk categories after screening by maternal age, fetal nuchal translucency, fetal heart rate, maternal serum free  $\beta$ -human chorionic gonadotropin and pregnancy-associated plasma protein-A<sup>13</sup>. The patients with a risk of 1 in 50 or more are considered to be screen positive and those with a risk of less than 1 in 1000 are screen negative. The patients with an intermediate risk of 1 in 51 to 1 in 1000 have second-stage screening with examination of the nasal bone, which modifies their risk. If the adjusted risk is 1 in 100 or more the patients are considered to be screen positive and those with a risk of less than 1 in 100 are screen negative. The last column lists the overall detection and false-positive rates. All percentages are adjusted according to the maternal age distribution of pregnancies in England and Wales in 2000–2002<sup>17</sup>.

serum PAPP-A and serum free  $\beta$ -hCG and after standardization for the maternal age distribution of pregnancies in England and Wales in 2000–2002, was 1 in 50 or higher in 1.6% of the euploid pregnancies and in 85.4%, 88.4%, 100% and 100% of those with trisomies 21, 18 and 13 and Turner syndrome, respectively (Table 6). Total risks of 1 in 51 to 1 in 1000 were found in 14.6% of the euploid pregnancies and in 13.4%, 11.6%, 0% and 0% of those with trisomies 21, 18 and 13 and Turner syndrome, respectively. Total risks of less than 1 in 1000 were found in 83.8% of the euploid pregnancies and in 1.2%, 0%, 0% and 0% of those with trisomies 21, 18 and 13 and Turner syndrome, respectively. The results for the validation dataset are also summarized in Table 6.

A contingent policy (where screen positivity is defined as either a first-stage total risk of 1 in 50 or higher based on maternal age, fetal NT, FHR, serum PAPP-A and serum free  $\beta$ -hCG or a risk of 1 in 100 or higher after assessment of the nasal bone in those cases where the first-line sum risk is between 1 in 51 and 1 in 1000) would detect 92.8% of all cases with trisomy 21 for a false-positive rate of 2.4% (Table 6). In the validation dataset contingent screening would detect 91.7% of all cases with trisomy 21 for a false-positive rate of 2.9%.

## DISCUSSION

The findings of this prospective screening study demonstrate that at 11–13 weeks there is absence of the nasal bone in 1–2% of euploid fetuses, in 60% of fetuses with trisomy 21 and in about half of fetuses with trisomies 18 and 13. These findings are consistent with the results of previous screening studies<sup>11,18–22</sup>.

Effective first-trimester screening for trisomy 21 is provided by a combination of maternal age, fetal NT thickness, FHR and maternal serum free  $\beta$ -hCG and PAPP-A. With a risk cut-off of 1:100 for the total risk for trisomy 21, 18, 13 and Turner syndrome, the detection and false-positive rates in screening for trisomy 21 were 3.0% and 91%, respectively. By assessing the nasal bone in all pregnancies the false-positive rate can be reduced by 17% to 2.5% without affecting the detection rate.

The prevalence of absent nasal bone is affected not only by the fetal karyotype but also by maternal ethnicity, being higher in Black than in White women, is inversely related to fetal CRL and serum PAPP-A and increases with fetal NT. Consequently, the prevalence of absent nasal bone will vary in different populations depending on ethnic mix and distribution of CRL, NT and PAPP-A. The prevalence of absent nasal bone in euploid fetuses in the study population was higher than in the validation population (2.6% vs. 0.6%) mainly because in the study population the prevalence of women of non-White ethnic origin was higher (20% vs. 6%).

In the development of an algorithm for the calculation of patient-specific risks for chromosomal abnormalities we used logistic regression analysis to take into account the maternal characteristics. Inclusion of the nasal bone improved the performance of first-trimester combined screening. At a risk cut-off of 1:100, the false-positive rate was reduced from 3.0% to 2.5% without decreasing the detection rate. The results in the algorithm development group were confirmed by applying this algorithm to a second large validation dataset.

Assessment of the nasal bone requires appropriate training of sonographers and adherence to a specific

technique for imaging the fetal profile. The ultrasound transducer should be parallel to the direction of the nose in the exact mid-sagittal plane. This plane is defined by the presence of the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the center and the nuchal membrane posteriorly<sup>23</sup>. A rotation from the exact midline plane by about 10° causes non-visualization of the tip of the nose and appearance of the zygomatic bone as an echogenic structure between the nasal bone above and the anterior part of the maxilla below. With further rotation by about 15° from the midline the nasal bone becomes non-visible and there is enlargement of the zygomatic bone.

A good sonographer experienced in NT scanning requires on average to carry out 80 scans of the nasal bone in order to become competent in this examination<sup>24</sup>. At present the availability of sonographers with such competence is limited. As demonstrated by the findings of our study assessment of the nasal bone need not be undertaken in all pregnancies undergoing routine first-trimester combined screening, but only in the 15% of the total population with an intermediate risk (between 1 in 51 and 1 in 1000) after combined testing. A two-stage screening policy would detect about 93% of all cases with trisomy 21 for a false-positive rate of 2.4%. Consequently, assessment of the fetal nasal bone improves the performance of first-trimester screening for trisomy 21, irrespective of whether this examination is carried out in all patients or only in one sixth of the total.

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