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Articles

Absence of nasal bone in fetuses with trisomy 21 at 11-14 weeks of gestation: an observational study

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Summary

Background Prenatal diagnosis of trisomy 21 requires an invasive test in women regarded as being at high risk after screening. At present there are four screening tests, and for a 5% false-positive rate, the sensitivities are about 30% for maternal age alone, 60-70% for maternal age and second-trimester maternal serum biochemical testing, 75% for maternal age and first-trimester fetal nuchal translucency scanning, and 85% for maternal age with fetal nuchal translucency and maternal serum biochemistry at 11-14 weeks. In this study, we examined the possible improvement in screening for trisomy 21 by examining the fetal nasal bone with ultrasound at 11-14 weeks of gestation.

Methods We did an ultrasound examination of the fetal profile in 701 fetuses at 11-14 weeks' gestation immediately before karyotyping for a possible chromosomal abnormality detected by maternal age and fetal nuchal translucency screening. The presence or absence of a nasal bone was noted.

Findings The fetal profile was successfully examined in all cases. The nasal bone was absent in 43 of 59 (73%) trisomy 21 fetuses and in three of 603 (0.5%) chromosomally normal fetuses. The likelihood ratio for trisomy 21 was 146 (95% CI 50-434) for absent nasal bone and 0.27 (0.18-0.40) for present nasal bone. In screening for trisomy 21, by a combination of maternal age and fetal nuchal translucency, we estimated that inclusion of examination of the fetal profile for the presence or absence of nasal bone could increase the sensitivity to 85% and decrease the false-positive rate to about 1%.

Interpretation In screening for trisomy 21, examination of the fetal nasal bone could result in major reduction in the need for invasive testing and a substantial increase in

sensitivity.

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Introduction

In 1866, Langdon Down noted that common characteristics of patients with trisomy 21 were poor skin elasticity, which gave the appearance of it being too large for the body, and flat face with a small nose.¹ We now know that the excess skin of individuals with trisomy 21 can be visualised by ultrasonography as increased nuchal translucency in the third month of intrauterine life.^{2,3} Measurement of fetal nuchal translucency thickness at 11-14 weeks of gestation has become an effective method of early screening for trisomy 21. In a multicentre study involving about 100 000 pregnancies, the sensitivity was 82.2% and the false-positive rate was 8.3%.³

In this observational study, we report the use of the second observation of Langdon Down--nasal hypoplasia--in early prenatal screening for trisomy 21.

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Methods

The study was done in our centre between January and October, 2001, on 701 fetuses at 11-14 weeks of gestation. There were 685 singleton pregnancies and eight dichorionic twin pregnancies, in which both fetuses were examined. All fetuses had been found to have possible chromosomal defects after screening with a combination of maternal age and fetal nuchal translucency thickness.³ After counselling, the parents had elected to have invasive testing.

We examined the fetal profile and noted the presence or absence of the nasal bone at the routine ultrasound scan done before chorionic villus sampling for fetal karyotyping. For examination of the fetal nose, a mid-sagittal view of the fetus was obtained, with the beam of the ultrasound transducer being parallel to the nasal bone (figure). In this position, the skin of the nose produces an echogenic line, which can be misinterpreted as the nasal bone. To avoid this mistake, the ultrasound transducer was gently tilted from side to side to ensure that the nasal bone was seen separate from the nasal skin.



Fetal profiles at 12 weeks of gestation in a normal fetus, showing the nasal bone, and a trisomy 21 fetus, showing absence of the nasal bone

Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of the examination. When the results of fetal karyotype were made available, they were also entered in the database.

The frequency of an absent nasal bone in the chromosomally normal and abnormal fetuses was noted, and the likelihood ratios for trisomy 21 in the presence and absence of the nasal bone were calculated. The Mann-Whitney *U* test was used to calculate the significance of differences in the median maternal age, nuchal translucency thickness, and crown-rump length in trisomy 21 fetuses with and

without a visible nasal bone.

To measure the potential effect of examining the nasal bone on screening for trisomy 21, we used data from a multicentre study of screening by maternal age and fetal nuchal translucency thickness, which involved 326 fetuses with trisomy 21 and 95 476 chromosomally normal fetuses.³ A computerised random-number generator was used to assign the same proportion of fetuses with absent nasal bone found in our study to the cases in the multicentre study. In each case, the estimated risk for trisomy 21 by maternal age and fetal nuchal translucency thickness was multiplied by the appropriate likelihood ratio for presence or absence of the nasal bone. The distribution of new risks in the trisomy 21 and normal fetuses was calculated, as were the sensitivity and false-positive rates for different risk cutoffs.

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Results

The median maternal age was 38 years (range 17-48), the median fetal crown-rump length was 65 mm (45-84), and the median gestation was 12 weeks (11-14). Examination of the fetal profile was possible in all cases. The nasal bone was not visible in three of 603 chromosomally normal fetuses, 43 of 59 with trisomy 21, 11 of 20 with trisomy 18, two of eight with Turner's syndrome, and in none of those with trisomy 13 (n=4), triple X syndrome (n=4), Klinefelter's syndrome (n=2), or triploidy (n=1).

In cases of trisomy 21, there was no significant difference between those with and without a visible nasal bone in terms of maternal age ($p=0.83$), nuchal translucency thickness ($p=0.79$), or crown-rump length ($p=0.75$, table 1). The likelihood ratio for trisomy 21 was 146 (95% CI 50-434) in the absence of nasal bone, and 0.27 (0.18-0.40) in the presence of the bone.

	Trisomy 21 (n=59)		Normal karyotype (n=603)	
	Nasal bone absent	Nasal bone present	Nasal bone absent	Nasal bone present
Number of cases	43 (73%)	16 (27%)	3 (0.5%)	600 (99.5%)
Median (range) maternal age (years)	38.9 (29.0-45.6)	39.3 (28.9-44.1)	22, 38.2, 39*	38.2 (28.6-45.9)
Median (range) nuchal translucency (mm)	4.2 (1.6-10.3)	4.05 (2.5-9.5)	2.1, 1.7, 2.2*	2.0 (0.8-5.6)
Median (range) crown-rump length (mm)	64.6 (50.2-82.5)	63.2 (49.1-75.7)	64.1, 58.3, 59.5*	65.0 (46-84)

*Individual values in the three cases with normal karyotype and absent nasal bone.

Table 1: Rate of absence or presence of nasal bone in trisomy 21 and chromosomally normal fetuses at 11-14 weeks

In the multicentre study, the estimated risk of trisomy 21 by maternal age and fetal nuchal translucency thickness was 1 in at least 300 in 82.2% (268 of 326) of trisomy 21 fetuses, and in 8.3% of (7908 of 95 476) chromosomally normal fetuses.³ If the nasal bone was examined in all fetuses at the time of measuring the nuchal translucency thickness, and the appropriate likelihood ratio was applied to the estimated risk of trisomy 21 by maternal age and fetal nuchal translucency thickness,³ the new risk would be 1 in at least 300 in 92.0% (300 of 326) of trisomy 21 fetuses and in 3.0% of (2887 of 95 476) chromosomally normal fetuses. Table 2 compares the sensitivity and false-positive rate for estimated risk cutoffs in screening by maternal age and nuchal translucency thickness with those of screening by maternal age, nuchal translucency thickness, and presence or absence of the nasal bone. We have previously shown that some of the trisomy 21 pregnancies identified

prenatally would have resulted in spontaneous miscarriage, had the parents not elected termination of pregnancy. Consequently, the effect of antenatal screening on the livebirth incidence of trisomy 21 is about 3% lower than that suggested by these sensitivities.^{3,4}

Risk cutoff	Nuchal translucency screening		Nuchal translucency and nasal bone screening	
	Sensitivity (%)	False-positive rate (%)	Sensitivity (%)	False-positive rate (%)
1 in 20	57.36	0.98	81.90	0.62
1 in 35	62.88	1.35	85.89	1.02
1 in 50	65.03	1.76	86.81	1.30
1 in 100	72.09	3.01	88.65	1.64
1 in 150	74.54	4.32	89.26	1.98
1 in 200	77.30	5.71	90.18	2.37
1 in 250	80.67	7.08	91.41	2.68
1 in 300	82.21	8.28	92.02	3.02
1 in 500	85.58	14.00	92.94	4.37
1 in 1000	92.33	27.40	94.79	8.15

Table 2: Estimated sensitivity and false-positive rate for risk cutoffs in screening for trisomy 21 by maternal age, nuchal translucency thickness, and presence or absence of the nasal bone by comparison with the results obtained in a multicentre study of screening by maternal age and fetal nuchal translucency thickness

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Discussion

This study has shown that, at 11-14 weeks of gestation, the nasal bone is visible by ultrasonography in 99.5% of chromosomally normal fetuses. This finding is compatible with the results of histological and radiological studies of aborted fetuses, which showed that the nasal bones first appear at a crown-rump length of 42 mm and increase linearly with gestation.⁵

In 73% of trisomy 21 fetuses, the nasal bone was not visible at the 11-14-week scan. This finding might be the consequence of hypoplasia or delayed ossification of the nasal bone. The growth of bone is dependent on the surrounding functional matrix,⁶ and immunohistochemical studies of the skin of trisomy 21 fetuses have shown alterations in the composition of the extracellular matrix, which might be attributed to gene dosage effects.⁷⁻⁹ For example, trisomy 21 is associated with a substantial increase in hyaluronic acid,⁹ which could be the consequence of increased superoxide dismutase, which is encoded in chromosome 21 and protects against free-radical-mediated degradation of hyaluronic acid. Similarly, the dermis of trisomy 21 fetuses is rich in collagen type VI and the genes for two of the three polypeptide chains of this collagen are found on chromosome 21.⁷

In trisomy 21, absence of the nasal bone is not related to the nuchal translucency thickness, and therefore these two sonographic markers can be combined relatively simply to provide a more effective method of early screening for trisomy 21. We estimated that if examination of the fetal profile for the presence or absence of the nasal bone is incorporated in screening for trisomy 21 by a combination of maternal age and fetal nuchal translucency thickness, the sensitivity would increase and the false-positive rate would decrease. For a fixed false-positive rate of about 1%, the

sensitivity could increase from about 57% to 86% and the respective sensitivities for a false-positive rate of 5% would be about 75% and 93% (table 2).³

Prenatal diagnosis of trisomy 21 requires an amniocentesis or chorionic villus sampling, which carry a 1% risk of causing miscarriage, in women regarded as at high risk after screening. At present there are four screening tests and, for a 5% false positive rate, the sensitivities are about 30% for maternal age alone, 60-70% for maternal age and second-trimester maternal serum biochemical testing, 75% for maternal age and first-trimester fetal nuchal translucency scanning, and 85% for maternal age with fetal nuchal translucency and maternal serum biochemistry at 11-14 weeks.^{3,10-15} The findings of the present study suggest that examination of the fetal profile at 11-14 weeks could have major beneficial implications in screening for trisomy 21 by maternal age and fetal nuchal translucency. The increase in sensitivity from 75% to 85% could be achieved with a simultaneous reduction in the false-positive rate from 5% to about 1% and a consequent five-fold reduction in the rate of miscarriage from invasive testing and the cost of invasive testing and analysis. Additionally, for a false-positive rate of 1%, a sensitivity of more than 90% could probably be achieved by the combination of nasal bone, nuchal translucency thickness, and first-trimester maternal serum biochemistry. However, we should not speculate on the precise rates before we examine the possible association between absence of the nasal bone and maternal serum markers.

As is the case for the nuchal translucency scan, sonographers undertaking risk-assessment by examination of the fetal profile must receive appropriate training and certification of their competence in doing the nasal bone scan. Furthermore, screening and risk assessment based on the presence or absence of the nasal bone should not be incorporated into routine screening before confirmation of our results by multicentre screening studies, one of which is in progress.

Contributors

Kypros Nicolaides was responsible for the study concept; Jiri Sonek developed the method of examining the fetal nose; Simona Cicero, Patrizia Curcio, and Aris Papageorghiou collected and analysed data; and all investigators contributed to the writing of the paper.

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