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Is Noninvasive Prenatal Screening Appropriate for Pregnant Women Age 35 or Older In Cases if Isolated Fetal Nasal Bone Abnormalities in The Chinese Han Population?

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Ethnic background may affect the prevalence of nasal bone absence and the length of the nasal bone. This study aimed to elucidate the significance of absent or hypoplastic fetal nasal bone in the Chinese Han population and to formulate an optimal management plan for patients age 35 or older in cases of isolated abnormal fetal nasal bone.

Material/Methods: We prospectively assigned pregnant women whose fetuses had nasal bone absence or hypoplasia to separate groups according to their choice for noninvasive prenatal screening (NIPS) between January 1, 2013, and December 31, 2018. Demographic data, ultrasound findings, results of conventional maternal serum screening and NIPS, fetal karyotype, pregnancy outcomes, and expenses associated with prenatal testing were recorded. The incidence and odds ratio of nasal bone abnormality and the sensitivity and specificity of different prenatal genetic screening tests were calculated.

Results: A total of 1946 cases with fetal nasal bone absence or hypoplasia were included. Cases of isolated nasal bone abnormality (1736 cases) were divided into the NIPS group (Gr 1, n=429) and the non-NIPS group (Gr 2, n=1307). Sixty-four cases involved chromosomal abnormality. The sensitivity, specificity, and positive and negative predictive values of NIPS in Gr 1 were 100%, 100%, 100%, and 100%, respectively. The odds ratio of fetal chromosomal abnormalities for isolated fetal nasal bone abnormalities when maternal age was ≥35 was 4.615 (95% CI: 1.592-13.381). The cost-effectiveness ratio of contingent screening (NIPS first) was significantly lower than amniocentesis directly.

Conclusions: The nasal bone provides an important marker for chromosome abnormalities in some populations, but to a lesser extent in the Chinese Han population. NIPS is an excellent first option for follow-up among pregnant women age ≥35 in cases of absent or hypoplastic fetal nasal bone in the first trimester ultrasound scan.

MeSH Keywords: Chromosome Aberrations • Nasal Bone • Prenatal Diagnosis • Ultrasonography, Prenatal

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Background

Langdon Down first reported a patient with trisomy 21 with flat face and small nose in 1866 [1], and it is now widely accepted and fully validated that specific facial features are associated with chromosomal abnormalities. Numerous studies have demonstrated that the absence or hypoplasia of nasal bone may be one of the strongest ultrasound markers for trisomy 21 and other aneuploidies in both the first and second trimesters [2]. The likelihood ratio of nasal bone abnormality for Down syndrome has been proven to be 24.1-146 in the first trimester [2–4] and 11.6-66.75 in the second trimester [2,5,6]. Therefore, nasal bone evaluation has become part of routine prenatal screening for fetal abnormities in the first and second trimesters. With such a high likelihood ratio, many obstetricians may suggest amniocentesis or chorionic villus sampling to pregnant women when fetal nasal bone abnormalities are present.

However, the ethnic background should be taken into consideration because the prevalence of nasal bone absence and the length of the nasal bone vary by ethnicity. In 1893, Manouvrier reported that ethnic variations in the nasal bone are related to interorbital distance, the width of the nasal notch, and the height of the face [7]. Many studies have found a higher incidence of nasal bone absence or hypoplasia, shorter nasal bone length, and a lower likelihood ratio for trisomy 21 in an Afro-Caribbean population [8–10]. Similarly, Wong et al. [11] reported that the nasal bone is absent in 0.88% of normal Chinese fetuses in the first trimester. In addition, Leung et al. [3] reported that the positive likelihood ratio for trisomy 21 based on abnormal nasal bone in the Chinese Han population was significantly lower than in Caucasians, with the ratio being almost half that found in the latter.

Nevertheless, prenatal diagnostic testing remains necessary for the Chinese Han population when fetal nasal bone absence or hypoplasia is detected. In 2011, Ting et al. [12] suggested that isolated absent or hypoplastic nasal bone did not indicate an increased risk for Down syndrome, but amniocentesis was indicated for fetuses with nasal bone abnormalities combined with another structural abnormality or additional soft marker. However, that study had a relatively small sample size (only 14). With the application of cell-free DNA (cfDNA) screening, or so-called noninvasive prenatal screening (NIPS), in recent years, the advice on follow-up for fetal nasal bone abnormalities in Chinese Han population might be prudently reconsidered.

The aim of this study was to elucidate the significance of nasal bone abnormalities as a marker for fetal chromosomal abnormalities in pregnant Chinese Han women in the first trimester and to explore the optimal management upon discovery of such abnormalities.

Material and Methods

The study was conducted from January 2013 to December 2018 at Women's Hospital, Zhejiang University, School of Medicine in Hangzhou, China. The study was approved by the ethical committee of Zhejiang University, and written informed consent was obtained from all patients. All pregnant Chinese women with ultrasound findings of fetal nasal bone abnormalities (defined as nasal bone length <5th percentile of Chinese population [13]) in the first trimester at 11–13+6 weeks during the study period were included. Women with multiple pregnancies, those belonging to ethnic minority groups, and those who did not give birth or induce labor in our hospital were excluded.

The procedure for prenatal screening was as follows. Pregnant women would get their first prenatal screening ultrasound at 11–13+6 weeks for nuchal translucency (NT), nasal bone, and the pattern of blood flow through the ductus venosus. Conventional maternal serum screening (CMSS) followed at 15-20 weeks, using the combination of maternal age, human chorionic gonadotropin, α-fetoprotein, and estriol. If the results were positive, NIPS or diagnostic prenatal testing was performed. Normally, pregnant women with maternal age ≥35 years old had 2 choices: (i) a contingent screening strategy in which NIPS was done first, with diagnostic prenatal testing conducted if the result was positive, or (ii) invasive prenatal diagnosis tests done directly. After 2015, patients were offered chromosomal microarray analysis (CMA) when invasive prenatal diagnostic testing was arranged. From 2013 to 2018, NIPS cost USD 151.44 per person, karyotyping in amniocentesis/fetal blood sampling cost USD 438.23 per person, and CMA cost USD 946.81 in our hospital. The cost of CMSS was covered by insurance, while NIPS and invasive prenatal diagnosis tests were all covered by patients.

A second ultrasound was performed at 20-24 weeks to screen for structural deformity and nasal bone abnormalities and other soft markers, including cerebral ventriculomegaly ≥10 mm, nuchal fold ≥6 mm, intestinal hyperechogenicity, short femur or humerus, echogenic intracardiac focus, choroid plexus cyst, mild renal pyelectasis ≥5 mm, absence of the middle phalanx of the 5th digit, and short mandible. All scans were performed by certified sonographers. If pregnant women received normal NIPS results and were later found to have ultrasonographic abnormalities, they would receive consultation in our Prenatal Diagnosis Unit and be offered further fetal cytogenetic analysis.

Pregnant women with isolated abnormal nasal bone detected in their fetus at the first prenatal screening ultrasound were assigned to either the NIPS group (Gr 1) and non-NIPS group (Gr 2) depending on their choice of the first genetic test. Gr 2 included pregnant women who chose to do either CMSS first or elected to proceed directly to diagnostic testing by amniocentesis.

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Table 1. Characteristic of cases with fetal nasal bone absence or hypoplasia.

Variable		Result (median/mean±SD)	Range
Age (years)		31	21–48
CRL (mm)		68	37–86
NT (mm)		1.5±0.8	
Gravidity (n)		2	1–10
Parity (n)		0	0–4
TOP (n)		77	
	Chromosome abnormality	60	
	Non-chromosome abnormality	13	
	Other reasons	4	
Miscarriage (n)		23	
Birth (n)		1746	
	Birth weight(g)	3309±429	
	Gestational weeks at delivery	39	28–41

TOP – termination of pregnancy; other reasons for TOP – pregnancy complications such as preeclampsia, pregnant with mental disease or mother's unwillingness to proceed pregnancy.

Demographic data, ultrasound findings from the first and second trimester scans, and obstetric outcomes of all cases including age, NT, CMSS results, and genetic test results were collected, and costs of prenatal screening/diagnosis were documented.

Statistical analysis

Statistical analysis was performed using the Statistical Packages of Social Sciences for Windows, version 22.0 (SPSS, Chicago, IL, USA). A P value of <0.05 was considered statistically significant. Continuous variables are presented as mean±standard deviation. Categorical variables are presented as numbers and percentages. Chi-square test or student *t* test was used to compare differences between groups, and 95% confidence intervals (CIs) were calculated where appropriate.

The odds ratio (OR) of fetal chromosomal abnormalities among cases of isolated abnormal fetal nasal bone associated with maternal age ≥35 years was calculated. The cost-effectiveness ratios of different screening strategies for older women were calculated. These ratios were then compared in terms of the cost per chromosomal abnormality averted. Sensitivity, specificity, and positive and negative predictive values of CMSS and NIPS for ruling out chromosomal abnormalities in the population with abnormal nasal bone was calculated. Sensitivity was defined as the ratio of the correctly classified positive tests to the total number of positive samples, while specificity was defined as the ratio of the correctly classified negative tests to the total number of negative results. The positive predictive value was the proportion of positive test results that were true positives, while the negative predictive value was defined as the proportion of negative test results that were correctly diagnosed.

Results

During the period from January 2013 to December 2018, 60 289 pregnant women underwent ultrasound scans at 11–13+6 weeks of gestation in our outpatient department. Examination of the fetal profile was satisfied in all cases. Among them, 4487 cases with abnormal nasal bone were found, including nasal bone absence and hypoplasia. The incidence rate of abnormal fetal nasal bone in our prescreened population was 7.4% (4487/60 289).

Of the 4487 cases, 430 cases were multiple pregnancies, including twins and triplets, and 2111 cases did not deliver in our hospital. Thus, the total number of abnormal nasal bone cases included in the study was 1946, of which, 1900 cases showed nasal bone hypoplasia and 46 cases showed nasal bone absence. The median maternal age was 31 years (range 21 to 48), the median gestational weeks at examination was 12.8 weeks (range 11 to 14), and the median fetal crown-rump length was 63 mm (range 37 to 86). Details are shown in Table 1 and Figure 1.

Among the 1946 cases, chromosomal abnormality was diagnosed in 64 cases, including 37 cases of trisomy 21, 4 cases of trisomy 18, and 1 case of trisomy 13, and other cases including 5 cases of microdeletion or microduplication. Sixty-seven cases had additional ultrasound findings in the first scans; of these,

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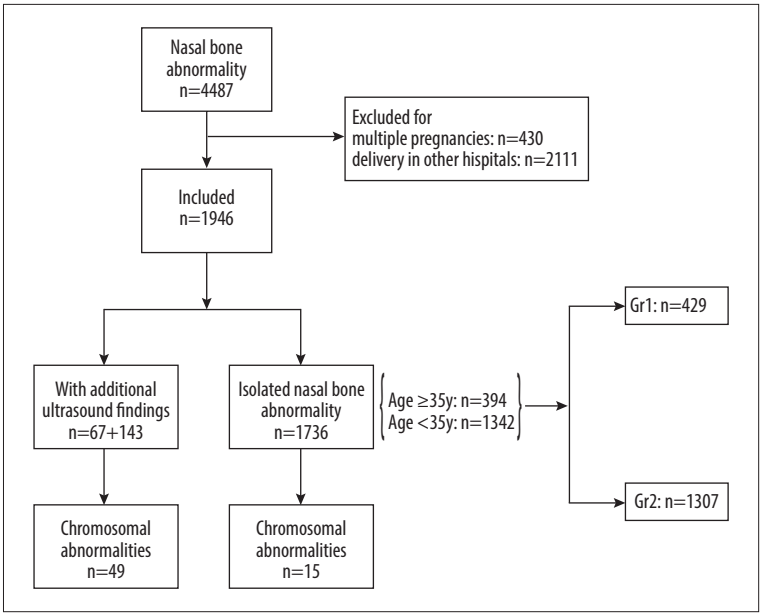

Figure 1. Flowchart showing participation, exclusion, and groups in the study.

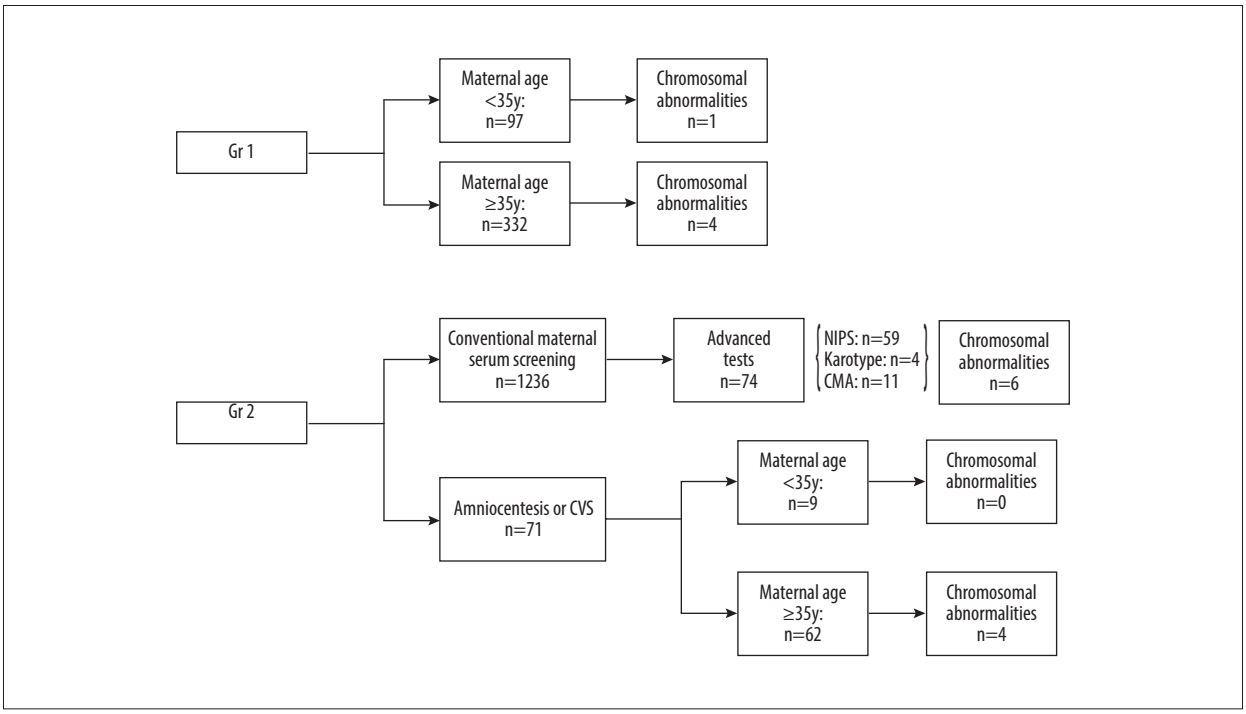

Figure 2. Detailed information of the 2 study groups.

35 cases had a chromosomal abnormality. In the other 1879 cases, 143 cases had additional ultrasound findings in the second scans at 20-24 weeks, and 14 cases had a chromosomal abnormality. In the remaining 1736 cases with isolated nasal bone abnormality, 15 cases (0.9%) had a chromosomal abnormality. Thus, nasal bone absence or hypoplasia in association with other structural malformation had a higher rate of abnormal karyotypes compared with isolated nasal bone abnormalities {23.8% [(35+14)/(67+143)] *vs.* 0.9%, chi-square test, P<0.01} (Figure 1).

Among the 64 cases with a chromosomal abnormality, 36 cases (56%) were prenatally diagnosed and the pregnancy was terminated before 20 weeks, while the other 28 cases were diagnosed and the pregnancy was terminated after the second scans at 20–24 weeks. There were only 25 cases of fetal nasal bone hypoplasia or absence found during the second scans, though.

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Table 2. Evaluation of NIPS and conventional maternal serum screening in nasal bone abnormality population.

	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
CMSS	1	68	1162	5	17%	94.47%	1.45%	99.57%
NIPS	5	0	424	0	100%	100.00%	100.00%	100.00%

TP – true positive; FP – false positive; FN – false negative; TN – true negative; PPV – positive predictive value; NPV – negative predictive value; NIPS – non-invasive prenatal screening; CMSS – conventional maternal serum screening.

Table 3. Cost-effectiveness ratio of two screening strategies in pregnant women older than 35.

strategies	Costs (USD)	Effectiveness (CA detected)	Cost per CA detected (USD)
Contingent screening strategy	63143.74	8	7893.86
Invasive diagnostic test	170999.41	8	21377.34

CA – chomosomal abnormalities. The costs were calculated based on pregnant women older than 35(n=394). The cost of invasive diagnostic test was calculated as karyotyping or CMA.

In the study, 1736 cases with isolated abnormal nasal bone belonged to either the NIPS group (Gr 1) or the non-NIPS group (Gr 2). Gr 1 had 429 patients, and Gr 2 had 1307 patients. The details are shown in Figures 1 and 2. The sensitivity, specificity, and the positive and negative predicative values of CMSS were 17%, 94.47%, 1.45%, and 99.57%, respectively. The sensitivity, specificity, and the positive and negative predicative values of NIPS were 100%, 100%, 100%, and 100%, respectively (Table 2).

Among the 394 cases of pregnant women with advanced maternal age (≥35 years), 332 patients chose NIPS, while 62 patients chose invasive prenatal tests directly (Figure 2). There were 8 cases of chromosomal abnormalities, including 2 cases of trisomy 21, 1 case of trisomy 18, 2 cases of sex chromosome aneuploidies (47, XXY), and 3 cases of microdeletion or microduplication. Among the cases with chromosomal abnormalities, 4 cases [trisomy 21*2, (47, XXY)*2] were indicated by NIPS first, with confirmation by invasive prenatal tests. The OR of fetal chromosomal abnormalities associated with isolated fetal nasal bone abnormalities was 4.615 (95% CI: 1.592–13.381) among women ≥35 years old.

We also calculated the cost-effectiveness ratio of contingent strategy and diagnostic tests directly in women with advanced maternal age. The cost of a contingent strategy to screen out a fetus with chromosomal abnormalities was significantly lower than directly choosing invasive prenatal diagnosis (USD 7893.86 *vs.* USD 21 377.34 per patient, P<0.0001; Table 3).

Discussion

The current study was performed in a large sample of women from the Han Chinese population. Most of the existing studies of fetal nasal bone abnormalities were carried out in high-risk populations, with a high prevalence of Down syndrome (7–20%) [9], which would absolutely increase the likelihood ratio of fetal nasal bone absence predicting trisomy 21. Many studies have confirmed that race has a substantial impact on the likelihood ratio [8–10]. The incidence rate of fetal nasal bone absence or hypoplasia in the first trimester in our study was 7.4%, which was higher than that reported by Prefumo et al. [10], who found incidence rates of 3.4% and 2.6% in Asian and white populations, respectively [10]. However, their study only included 609 Asian mothers, and the Asian group was not refined and may have been heterogeneous with regard to ethnic background. The incidence rate in our population was similar to that reported in an Afro-Caribbean population (9%) [8].

Nasal bone absence has been detected in 0.5–2.8% of euploid fetuses in either the first or second trimester [2,4,11], and some studies have suggested a relatively low occurrence of abnormal karyotype in association with isolated fetal nasal bone abnormalities [12,14]. To the best of our knowledge, our study describes the largest population of isolated fetal nasal bone abnormalities, and it strongly supports the conclusion from the previous studies. In the present study, the incidence of abnormal karyotype with an isolated nasal bone abnormality was 0.9% (15/1736), while in cases with the abnormality paired with other ultrasound findings, the rate increased to 23.3% (49/210).

Many studies draw more attention to the fetal nasal bone in the second trimester because its length increases with gestational age [4,15]. In our study, 56.2% (36/64) of pregnancies with chromosomal abnormalities were terminated after the first ultrasound scans. Therefore, we suggest that fetal nasal bone in the first trimester is more valuable for early identification

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of fetal chromosomal abnormalities. Early detection can allow early termination of a pregnancy, which may reduce the pain for pregnant women, both physically and emotionally. Most cases of fetal nasal bone hypoplasia were visible at the second scans in our study, which may be due to delayed ossification. However, other congenital anomalies may occur despite visible nasal bones, which indicates that nasal bone hypoplasia in the first trimester may have some measure of predictive value.

Strategies have been changed dramatically since the introduction of NIPS, which has been shown to have high efficacy in detecting aneuploidies. The sensitivity of NIPS approaches 99.7% for Down syndrome, 97.9% for trisomy 18, 99% for trisomy 13, and 93% for sex chromosome aneuploidies [16]. In the present study, we found that NIPS had very high specificity and positive and negative predicative value (100%), it was as effective as invasive prenatal tests, and it was far more effective than CMSS. However, because of the higher cost of NIPS in China, it cannot replace CMSS in low-risk pregnancies [17].

Age is an isolated risk factor for aneuploidy, particularly after age 35. For pregnant women age 35 or older, we calculated the odds ratio and confirmed the increased risk of isolated fetal nasal bone abnormalities with advanced maternal age. We also calculated the cost-effectiveness ratio of 2 screening strategies, and the contingent screening strategy was found to be an appropriate strategy to balance effectiveness and cost. Given that NIPS can be done as early as 10 weeks' gestation and could avoid the risk of miscarriages induced by diagnostic testing, the contingent screening strategy is a good choice for pregnant Chinese women who are 35 or older in cases of isolated fetal nasal bone abnormality.

We found 5 cases of microdeletion or microduplication through amniocentesis. Many studies have described cases of microdeletion or microduplication, such as B-cell immunodeficiency and cri du chat (5p-) syndrome, with abnormal nasal bone development [18]. Dukhovny et al. [19] studied 57 euploid fetuses with absent nasal bones and found 3 cases with adverse outcome: one with multiple congenital anomalies, a microdeletion syndrome, and one specific genetic diagnosis. Because CMA was applied only after 2015, it is highly likely that we underestimated the microdeletion rate in our study.

Our study has some limitations. First, our data only include patients who gave birth at our hospital. Second, although the whole sample was large, the number of pregnant women who were 35 or older was small. Third, the cost-effectiveness ratio was difficult to calculate based on our small cohort. It would be immensely valuable to conduct a larger prospective study in multiple centers in China to obtain more representative data and results.

Conclusions

Absent or hypoplastic nasal bone is highly associated with fetal chromosomal abnormalities, especially in the first trimester. However, isolated nasal bone absence or hypoplasia for trisomy 21 screening has been demonstrated to not be very efficient in the Chinese population. NIPS could provide credible information in screening for fetal chromosomal abnormalities and it costs less. It may be especially recommended in pregnant women who are 35 or older in cases of absent or hypoplastic fetal nasal bone.

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Conflicts of interest

None.

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