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ORIGINAL ARTICLE

Assessment of Fetal Nasal Bone Length and Nasofrontal Angle in the Second Trimester in Normal Indian Pregnancies

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Abstract The authors aimed to establish the reference ranges of fetal nasal bone length (NBL) in the second trimester and evaluate the relationship between fetal NBL and biparietal diameter (BPD) at 17–22 weeks of gestation in the Indian population. The authors also determined the normal ranges of the fetal nasofrontal angle (NFA). Ultrasound examination was done in 486 singleton pregnancies at 17–22 weeks of gestation. The fetal NBL was measured in millimeters in a strict sagittal view of the fetal head. The NFA was also measured in this mid-sagittal profile. The authors present the normal range of fetal NBL. Mean NBL was found to increase linearly with advancing gestation and BPD. The NBL appears to be marginally longer in Indian fetuses than other Asian fetuses. The minimum, maximum, and mean NFA values were 112, 142, and 130 degrees. The authors present the normal range of NBL in the second trimester in the Indian population and identify its linear relationship with gestational age. The normal range varies among races and so a relative percentile is a more reliable screening criterion than an absolute value. The authors present the normal ranges of fetal NFA from 18 to 21 weeks.

Keywords Ultrasonography · Nasal bone · Fetus

Introduction

The nasal bone is one of the important fetal structures to be evaluated in the first and second trimesters of a pregnancy. Many studies have demonstrated that the absence or hypoplasia of the nasal bone or a depressed nasal root may be associated with trisomy 18, trisomy 21, Apert syndrome, and Lange syndrome [1, 17]. One of the most common chromosomal abnormalities in newborns is trisomy 21 [2]. Many sonographic features have been studied for the detection of trisomy 21 in the last few decades [3]. Down syndrome is characterized by facial abnormalities including a flat facial profile and a small nose [4, 5].

Examining the fetal nasal bone length (NBL) could be useful in screening for trisomy 21 in the first and second trimesters. Maternal age, fetal nuchal translucency, inclusion of fetal profile for nasal bone can increase the sensitivity substantially and decrease the false positive rate of screening test for Down syndrome [6–8]. Morphometry of nasal bone differs according to ethnicity [9]. Reference ranges of normal NBL need to be identified for different races to introduce this marker into routine screening. For Caucasian, African–American, and South American populations, the normal ranges of fetal NBL have been established [10–13]. There is limited data regarding the reference range of NBL in Asian populations [14–16]. This study shows the findings on fetal NBL in Indian population in second trimester.

Apert syndrome shows marked depression of the nasal bridge as was studied by M. Michael Cohen and Sven Kreiborg [17]. Very few studies have been carried out on nasofrontal angle (NFA) [18, 19]. It was hypothesized that NFA measurement could be used as a potential parameter for screening of Down syndrome. In this study, the authors aimed to evaluate the nasal root and determine the normal range of the NFA, which may be potentially used as a predictor of the above mentioned syndromes or other congenital abnormalities associated with abnormal NFA.

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‘‘Depressed nasal root’’ is a subjective criterion that is determined by the experience and interpretation of the examining radiologist as reported by Ozturk et al. [18]. This study helps in giving definition to the term “depressed nasal root”.

Materials and Methods

The study was conducted in Acharya Vinoba Bhave Rural Hospital, Datta Meghe Institute of Medical Sciences (Deemed University), Sawangi (Meghe), Wardha after obtaining approval from Institutional Ethics Committee. The informed consent of the patients was taken before accepting them for the study. This was a prospective cross-sectional analytical study conducted from September 2011 to December 2013. Ultrasound examination was done in 486 singleton pregnancies from 17 weeks onwards till 22 weeks of gestation. These were studied on the same day every week sequentially. All of them were Indians and had an Indian partner. Gestational age (GA) was calculated based on the last menstrual period (LMP) in patients with known and regular periods. In case where either LMP was uncertain or the fetal biometry was dischordant, the GA was estimated by second trimester biometry. The fetal NBL was measured in millimeters in a strict sagittal view of the fetal head (Fig. 1). The angle between the insonation beam of the ultrasound and nasal bone axis was kept close to 45 or 135 degrees, following the method described by Sonek et al. [12]. The NBA was also measured in this mid-sagittal profile. After delivery, the infants were examined by pediatrician for any syndrome or abnormality. Ultrasound scans where fetal profile was unfavorable for NBL and NBA measurements, fetuses with known abnormal karyotypes, presence of major or minor fetal anomalies, polyhydramnios, oligohydramnios and intrauterine growth restriction, and deliveries outside the institution were excluded.

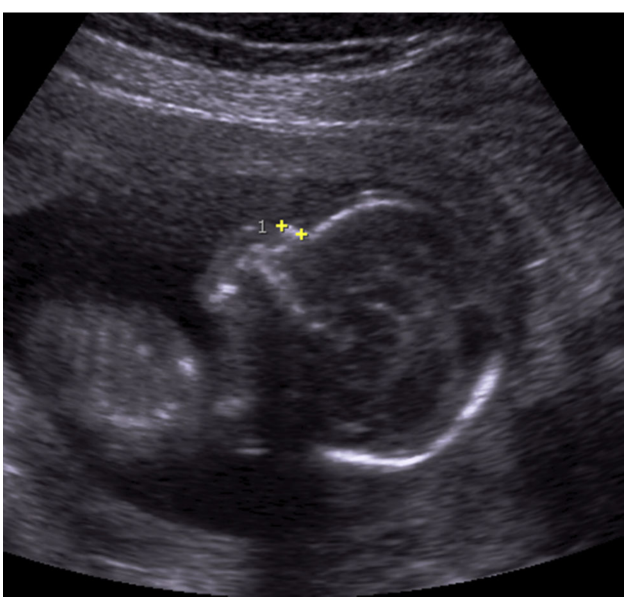

Fig. 1 A strict sagittal view of the fetal head used to measure the fetal nasal bone length and nasofrontal angle

Simple random sampling was used to recruit the samples and sample size was calculated by carrying out a pilot study. Allowance was made for noninclusion if fetal profile was unsatisfactory for measurements, so that this can be added on to the required sample size.

A total of 458 singleton pregnancies underwent ultrasound examination at 17–22 weeks of gestation. The fetal NBL and NFA was measured in a strict sagittal view of the fetal head.

The exact mid-sagittal plane of the fetal face is defined by the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the center and the nuchal membrane posteriorly. All ultrasound scans were performed transabdominally with a convex probe of 3–6 MHz. The magnification of the image was such that the head and upper thorax occupied the whole screen.

The NFA between the nasal bone and the frontal bone in the mid-sagittal plane was measured with the fetal neck was in mild flexion. The measurements in the 18th to 21st weeks were analyzed to search for an association between GA and NFA. The demographic characteristics and ultrasound findings were recorded prospectively on a data sheet. The relationship between NBL and GA was calculated. Postpartum evaluation was performed by experienced pediatricians, which included detailed physical examination.

Statistical Analysis

Statistical analysis was performed with a standard software package (SPSS for windows 11.0, Chicago, IL, USA), where a probability value of $p < 0.05$ was considered statistically significant. A descriptive analysis was performed for the demographic characteristics of the population. Mean ± SD and percentiles at 2.5th, 5th, 50th, 95th and 97.5th of fetal NBL were calculated from 17th to 22nd weeks. Distribution of the median NBL (mm) versus GA was calculated. Scattergram containing regression lines for NBL versus BPD was prepared for the study population. ANOVA was applied to test the difference of 50th percentile of Indian NBL from 17th to 22nd weeks with other Asian (Thai, Korean, Chinese and Japanese) measurements. A linear regression analysis was conducted in which NFA was entered as the response variable and fetal age as the predictor.

Table 1 Reference range of nasal bone length in the second trimester for normal Indian fetuses (n = 458)

Gestational age (weeks)	Mean ± SD	Percentile				
		2.5th	5th	50th	95th	97.5th
17	4.64 ± 0.42	2.90	2.90	3.70	5.30	5.40
18	4.86 ± 0.36	2.60	3.20	3.90	6.0	6.50
19	5.13 ± 0.37	1.80	3.90	5.40	6.20	6.30
20	5.68 ± 0.33	4.50	4.60	5.80	7.10	7.75
21	6.19 ± 0.30	5.10	5.80	6.70	7.20	7.6
22	6.98 ± 0.23	5.55	6.90	7.00	8.0	8.10

Results

Examination of the nasal bone was done in 458 fetuses and they were followed sequentially from 17th to 22nd week till delivery. The median maternal age was 23 years. There were no cases of absent or hypoplastic (less than 2.5 mm) nasal bones in the present study. Table 1 shows reference range of NBL in the second trimester for normal Indian fetuses (n = 458)

NBL increased linearly with advanced GA, with linear regression of the fetuses producing the equation:

$$\text{NBL} = -3.203 + \text{GA} \times 0.513.$$

Mean NBL was found to increase linearly with advancing BPD (Fig. 2), and was described by the equation:

$$\text{NBL} = 0.835 + 0.132 \times \text{BPD},$$
$$\text{R2} = 0.738, \ p < 0.001.$$

The 5th, 50th, and 95th NBL percentiles with respect to BPD are presented in Table 2. The median NBL was 5.8 mm between 17 to 18 weeks of gestation, and, as BPD increased from 35 to 55 mm, the median NBL increased from 5.8 mm to 7.4 mm (Table 2).

The minimum, maximum, and mean (±SD) NFA values were 112, 142, and 130 degrees (±6.6 degrees), respectively, in fetuses between the 18th and 21st gestational weeks. The 5th and 95th percentile values of NFA were 120 and 140 degrees, respectively (Table 3). Linear regression analysis showed no association between NFA and gestational week (Beta = 0.02; p = 0.79).

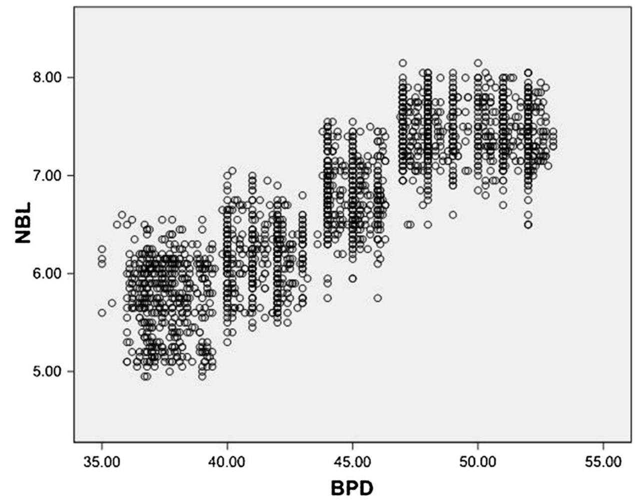

Fig. 2 Scattergram showing that mean nasal bone length increased linearly with advancing biparietal diameter

Table 2 Distribution of nasal bone lengths (mm) versus biparietal diameters (mm) from 17th to 22nd week of gestation

BPD (mm)	5th Percentile	Median	95th Percentile
35.0–39.9	5.10	5.80	6.30
40.0–44.9	5.65	6.35	7.15
45.0–49.9	6.45	7.25	7.85
50.0–54.9	7.00	7.40	7.90

Table 3 Nasofrontal angle values at the gestational age of 18 through 21 weeks in 458 fetuses

Gestational week	Nasofrontal angle (Degree)		
	Mean ± SD	Minimal	Maximal
18th week	123.87 ± 7.28	112	140
19th week	128.69 ± 6.68	114	140
20th week	131.64 ± 6.57	114	140
21st week	133.46 ± 6.50	116	142

Discussion

The nasal bones begin their development in the sixth week of gestation as collections of neural crest cells and become ossified through the process of intramembranous ossification. The nasal bone may be visualized on the mid-sagittal sonogram of the face after the tenth week of pregnancy and consists of two separate bones. The nasal bones first appear at a crown rump length (CRL) of 42 mm (11 weeks) as shown by histological and radiological studies of aborted fetuses [20].

It has been demonstrated that the absence of the nasal bone in the first trimester or its absence/hypoplasia and a depressed nasal root in the second trimester could be associated with chromosomal anomalies including trisomy 21. Nasal bones show a linear growth that parallels that of other bones. Odibo and colleagues reported that nasal bone size showed a linear increase between the 11th and 20th gestational weeks [21]. This linear development was also reported in the second and third trimesters.

If the nasal bone is not scanned in the correct plane, it may not be visualized or may be measured incorrectly. The resolution of the ultrasound equipment, experience of the operator and his interpretation, presence of oligohydramnios, obesity, the position of the fetus, and GA may affect the identification and measurement of the nasal bone [8, 10].

The parameters that have an impact on the efficacy of NBL-based screening for trisomy 21 are the ethnicity-related variations in NBL and nasal bone width during gestation [9–13]. A reference range for growth of the nasal bone from 14 to 34 weeks was initially presented by Guis et al. [10]. Many researchers like Bunduki et al. and Sonek et al. have then published many reports on the normal range of NBL throughout gestation [11, 12]. Nomograms of fetal NBL for Caucasian, African–American, and South American populations are available but there is only little research done on Asian populations [10–16].

In the Korean population [16], Shin et al. discussed the relation between NBL and biparietal diameter (BPD) where pregnancies referred for amniocentesis at 15–20 weeks including normal karyotypes were studied. Few studies in the Korean population have included abnormal karyotypes to evaluate the efficacy of NBL as a marker for trisomy 21 screening.

In the present study, the authors examined the NBL from 17 to 22 weeks. We provide the reference range of fetal NBL for the Indian population in the second trimester using a standardized technique. As in agreement with other researches, NBL increased linearly with GA.

It is ideal that research methods include a large data and analyze the mean values when statistical comparisons between different ethnicity and races need to be studied. Gamez et al. [13] reported longer nasal bone in Caucasians than that reported by E. Jung et al. in Korean population [22]. Most studies have only used median values in their analysis [13, 20].

Studies have pointed out that the median of the NBL in the Korean population seems to be smaller than in Caucasians and also smaller than in the Chinese [11, 12, 15]. The present study has shown a slightly longer NBL than Thai, Korean, Chinese, and Japanese suggesting that variations exist among races within Asian populations, although not statistically significant. To analyze the differences in NBL among races, larger prospective studies inclusive of fetuses of diverse ethnic origins need to be undertaken. Racial variability is also a factor to be considered before applying nomograms of NBL ultrasound examinations in clinical use.

There are racial differences in the prevalence and distribution of nasal bone hypoplasia in trisomy 21 and in normal fetal measurements. Absence of nasal bone in the first trimester varies in chromosomally normal fetuses among Africans (5.8 %), Caucasians (2.6 %), and Asians (3.4 %) as reported by Prefumo et al. [23]. The incidence of hypoplastic nasal bone among chromosomally normal Chinese fetuses was comparable with that seen in Caucasian fetuses [14, 21].

There is no uniformity in deciding the cut-off value to diagnose nasal bone hypoplasia in the second trimester (less than 2.5th percentile, 5th percentile, and 2.5 mm). Therefore, inter-study comparisons cannot be made [8, 11, 13, 22]. Jung et al. found that hypoplastic nasal bone was observed in 3.1 % of normal fetuses when the cut-off value was at the 2.5th percentile. However, it was 5.4 % when the cut-off value was kept at the 5th percentile [22].

To introduce it into routine screening, normal ranges of the NBLs as well as the cut-offs for a diagnosis of hypoplasia need to be defined for different races. It is better to use a percentile-based cut-off than an absolute value. Karyotyping was not done in the present study. Studies with a large sample size need to be carried out to establish the exact role of nasal bone hypoplasia in the screening for trisomy 21 in the Indian population.

Screening for trisomy 21 using the 5th percentile of the normal value as a cut-off value resulted in a sensitivity of 59.1 % among 1,693 singleton pregnancies scanned at 16–24 weeks of gestation [11]. However, the diagnosis of nasal bone hypoplasia requires facts of normative data for NBL across gestation. Moreover, normative data obtained from an unselected patient population should be preferred over data collected from high-risk patients or low-risk alone [19]. The present study provides normal fetal NBLs in the second trimester, and NBL distributions according to BPD in the Indian population.

A comparison of subgroups (African–American, Caucasian, South American, and Asian) suggests that median NBL distributions at 15–19.9 weeks vary by race. Thus, there is a need to construct a normative NBL range in the Indian population. The present study should be viewed as a preliminary study, which establishes a reference range and confirms the effects of racial differences. A multicenter study to define a normal reference range and NBL cut-off values in the Indian population is the need of the hour. Correct NBL measurements can be achieved by those who are adequately trained, given ongoing continuous quality control, and auditing. Such training is essential before prenatal nasal bone measurements can be applied to the detection of aneuploidy.

In the literature, there are only a few studies that have included NFA measurement, namely the study by Hasan Ozturk et al. in the second trimesters [18]. Hasan Ozturk et al. reported NFA that ranged from 110 to 143 degrees with a mean $\pm$ SD of 128 $\pm$ 7 degrees between the GAs of 18th and 21st weeks [18]. In the present study, the 5th and 95th percentile values of NFA were 120 and 144 degrees, respectively. The present study reflects similar findings of NFA as researched by other studies.

The NBL appears to be marginally longer in Indian fetuses than in other Asian fetuses. This indicates that the normal range would vary among races and that a relative percentile is a more reliable screening criterion than an absolute value. This study shows that the maternal ethnic origin affects the normal range of fetal NBL.

The authors found a linear relationship between fetal NBL and BPD in the second trimester, and a slightly longer NBL in Indian fetuses than in other Asian fetuses at commensurate GAs. More data are required to firmly establish the normal reference range and cut-off values, and larger studies are needed to establish the exact role of fetal nasal bone hypoplasia as a second-trimester ultrasonographic screening marker for trisomy 21 in the Indian population. The association between NFA measurements and various congenital anomalies/syndromes or fetal outcomes remains to be investigated.

Conflict of interest None.

Ethics committee approval The study was conducted after obtaining approval from Institutional Ethics Committee; vide reference Number DMIMS (DU)/IEC/2011-12/251.

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