Fetal nasal bone length at 11^{+0}- 13^{+6} weeks of gestation: an evaluation of 554 consecutive cases

A. Cansu[1], H. Ozgur[1], S. Guven[2], G. Dinc[3], H. Dinc[1]

[1]Department of Radiology, Karadeniz Technical University Faculty of Medicine, Trabzon
[2]Department of Obstetrics and Gynecology, Karadeniz Technical University Faculty of Medicine, Trabzon
[3]Clinic of Obstetrics and Gynecology, Trabzon Women and Children Hospital, Trabzon (Turkey)

Summary

Purpose of investigation: To develop a nomogram for estimating nasal bone length (NBL) at 11^{+0}- 13^{+6} weeks of gestation in 554 consecutive cases and to determine the value of NBL measurement in screening for chromosomal abnormalities. *Materials and Methods:* NBL and crown-rump length (CRL) were examined in 554 fetuses at 11^{+0}-13^{+6} weeks' gestation. A nomogram for NBL was developed with data from 479 healthy fetuses in which fetal profile examination was possible. Reference values, including percentiles, were calculated for each gestational age. *Result:* A linear correlation was noted between CRL and NBL in healthy fetuses at 11^{+0}-11^{+6}, 12^{+0}-12^{+6} and 13^{+0}-13^{+6} weeks of gestation. Mean NBL was 2.18 ± 0.53 mm, 2.46 ± 0.45 mm, and 2.91 ± 0.55 mm in healthy fetuses, for these time frames, respectively. NBL increased significantly with CRL from respective means of 2.26 ± 0.43, 2.60 ± 0.48, 2.77 ± 0.43, and 3.16 ± 0.52 mm at 45 - 54.9, 55 - 64.9, 65 - 74.9, and 75 - 84 mm. *Conclusion:* The authors developed a NBL nomogram with data from normal, healthy Turkish fetuses at 11^{+0}-13^{+6} weeks of gestation. These reference ranges may prove useful in prenatal screening and diagnosis of syndromes known to be associated with nasal hypoplasia.

Key words: Fetal nasal bone; Ultrasonography; Chromosomal abnormalities.

Introduction

Screening for fetal chromosomal abnormalities has become a very important part of prenatal fetal evaluation [1-3]. Nuchal translucency (NT) is the most commonly used sonographic parameter in first-trimester screening for chromosomal abnormalities [2, 3]. However, fetal nasal bone (NB) assessment has recently been proposed as an additional screening tool for fetal chromosomal abnormalities [1]. Cicero *et al.* [1] were the first to investigate the role of NB examination in first-trimester screening for trisomy 21. Several studies have noted a high prevalence of hypoplastic nasal bone in trisomy 21 fetuses at 11-14 weeks' gestation [4-6]. At screening for trisomy 21 by maternal age, examination of the fetal profile for the presence or absence of the NB can significantly increase sensitivity and reduce the false-positive rate [1, 7]. However, studies have revealed that NBL exhibits ethnic differences [8, 9]; the determination of NB hypoplasia may therefore depend on ethnicity.

The number of studies in Turkey on this issue is quite limited [10-12]. The aim of this study was to develop a nomogram for estimating nasal bone length (NBL) at 11^{+0}-13^{+6} weeks of gestation in a well-selected local Turkish population.

Materials and Methods

Fetal NB examinations were prospectively performed on 554 singleton pregnancies at the time of routine first-trimester screening (11^{+0}-13^{+6} weeks of gestation) in the Departments of Obstetrics and Gynecology and Radiology of the Karadeniz Technical University Faculty of Medicine during the four years of study period. Pregnant women were selected consecutively. The study was approved by the Karadeniz Technical University Faculty of Medicine Ethical Committee and informed consent was obtained from all patients. Gestational age was calculated using mothers' reports of the first day of the last menstrual period and subsequently confirmed by fetal crown-rump length (CRL) measurement. Sonographic examination was performed using an ultrasound scanner with a 1-4 MHz convex transducer. Approximately 25% of cases, in which transabdominal imaging was suboptimal because of inadequate fetal position or maternal obesity, were examined via a four to nine MHz transvaginal transducer. Examination of the fetal NB was incorporated in routine first trimester screening by CRL. In addition to the CRL and NB measurements, a detailed structural evaluation was performed on each fetus.

Examinations were performed by one of two authors. For examination of the fetal NB, a midline sagittal view of the facial profile was obtained at an insonation angle of approximately 45° when the fetuses were in the supine position. The fetal head, neck, and upper thorax were magnified until they filled the image area, and the ultrasound transducer was gently tilted from side-to-side to show three distinct lines the NB, the overlying skin, and the tip of the nose (Figure 1). The measuring calipers were placed in an out-to-out position, and the average of two measurements was used for analysis.

Following ultrasonography, patients were referred on the same day to the Karadeniz Technical University Medical Faculty Department of Obstetrics and Gynecology. All pregnant women with appropriate weeks of gestation were enrolled. Risk scanning was performed by combining mother's age and NT levels, beta-human chorionic gonadotropin studied from mothers' serum specimens and pregnancy-associated plasma protein-A values. Karyotype analysis was performed with amniocentesis by the relevant de-

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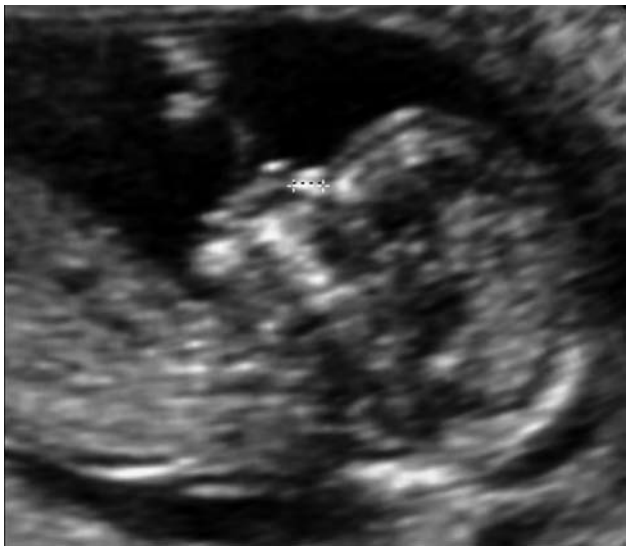

Figure 1. — Sonographic measurement of the nasal bone length using a midline sagittal view of the facial profile.

partment in 59 cases identified as at risk of chromosomal anomaly and whose families permitted the procedure. Karyotype results were recorded for those cases in which amniocentesis was performed. Perinatal outcome in the low-risk group was obtained from hospital records.

Exclusion criteria were abnormal karyotype, referral for suspected ultrasound anomaly, or fetal anomaly diagnosed at ultrasound examination or afterward, women having systemic disease (diabetes mellitus, hypertension, heart disease, etc.), women having obstetric complications or women having high risk pregnancy. Detailed ultrasonographic examination was performed in the second trimester for pregnant women included in the study. Ultrasound assessment of the fetal nasal bones was attempted in 583 fetuses. Thirty cases were excluded due to chromosomal and/or structural abnormalities. Examination of the fetal NB was not possible in 44 fetuses because visualization was inadequate due to inappropriate fetal position. One healthy fetus had no nasal bone and excluded for final analysis.

Statistical analysis was performed using SPSS. Data were analyzed via Pearson's correlation test, and R coefficients were calculated. Regression analysis was performed with NBL values and the biometric parameters; regression coefficients were calculated and regression equations produced. Mean and standard deviation NBL values were calculated according to the CRL and gestational age using data for healthy fetuses; a local nomogram was thus developed.

Results

CRL and NBL were measured in 479 healthy normal fetuses. Of these 479 fetuses, 36, 186, and 257 were evaluated at 11^{+0}-11^{+6}, 12^{+0}-12^{+6}, and 13^{+0}-13^{+6} weeks of gestation, respectively. Mean gestational age at time of sonographic evaluation was 12.32 ± 0.5 weeks. Mean age of the women was 31.34 ± 6.78 years, range, 17-45 years.

Nasal bone measurements to CRL are shown in Table 1. NBL of normal cases increased linearly with CRL increase;

Table 1. — *NBL measurements by CRL in healthy fetuses.*

CRL		NBL	
mm	n	(Mean±SD)	Min - Max
45-54.9	102	2.26±0.43	1.3 - 3.4
55-64.9	165	2.60±0.48	1.3 - 3.5
65-74.9	121	2.77±0.53	1.5 - 3.8
75-84	91	3.16±0.52	1.6 - 4.2

CRL: crown-rump length; NBL: nasal bone length.
n: number of fetuses in which measurement of NBL was possible.

Table 2. — *NBL measurements by gestational age in healthy fetuses.*

Gestational age (weeks)	n	NBL (mm)	
		(Mean±SD)	Min- Max
11^{+0}–11^{+6}	36	2.18±0.53	1.3 - 3.4
12^{+0}–12^{+6}	186	2.46±0.45	1.3 - 3.8
13^{+0}–13^{+6}	257	2.91±0.55	1.5 - 4.2

NBL: nasal bone length.
n: number of fetuses in which measurement of NBL was possible.

Table 3. — *Percentiles of NBL measurements by gestational age.*

Weeks	n	Percentiles						
		2.5%	5%	10%	50%	90%	95%	97.5%
11^{+0}–11^{+6}	36	1.3	1.4	1.4	2.2	3.1	3.3	3.4
12^{+0}–12^{+6}	186	1.6	1.8	1.9	2.5	3.3	3.4	3.6
13^{+0}–13^{+6}	257	2.2	2.3	2.4	2.9	4.0	4.1	4.2

n: number of fetuses in which measurement of NBL was possible.
NBL: nasal bone length.

a linear correlation was noted between CRL and NBL in healthy fetuses at 11^{+0}-11^{+6}, 12^{+0}-12^{+6} and 13^{+0}-13^{+6} weeks of gestation. Regression analysis between NBL and CRL revealed a regression equation of y = 0.781 + 0.030 x CRL, R = 0.533, $p < 0.001$, and a significant correlation was determined between CRL and NBL. Nasal bone measurements according to gestational age are listed in Table 2, while percentiles of these measurements by gestational age are shown in Table 3. Amniocentesis was performed in 59 fetuses for various reasons (advanced age of mother, maternal anxiety, family history of child with abnormal chromosomal anomaly, abnormal serum screening test, etc.) and revealed chromosomal abnormalities in 19. The results for the cases with chromosomal anomaly are given in Table 4.

Linear regression tables regarding NBL and gestation week and NBL and CRL are made in Figures 2 and 3. Regression analysis between NBL and CRL revealed a regression equation of y = 0.781 + 0.030 x CRL, R = 0.533, $p < 0.001$, and a significant correlation was determined between CRL and NBL. The 2.5 percentile from mean NBL was considered the cut-off point for hypoplasia. Fetuses were considered to have a hypoplastic NB when NBL fell below 2.5 standard deviations from mean NBL.

Table 4. — *Data for 19 cases with chromosomal anomaly.*

Case	*Age	CRL	Weeks	NBL	Karyotype	US findings	Prognosis
1	22	58	12	1,9	Trisomy 18	Anencephaly, spina bifida	Discharge
2	36	65	13	1,1	Trisomy 21	Hydrops	Discharge
3	32	70	13	2,4	Trisomy 18	Omphalocele, extremity anomalies	Discharge
4	35	77	12	0,0	Trisomy 18	Choroid plexus cyst, clubfeet	Discharge
5	25	65	12	2,8	Triploidy	Hydrops	IUEF, discharge
6	20	56	12	0,9	Trisomy 21	None	Unknown
7	36	60	12	absent	Trisomy 21	Hydrops	Discharge
8	34	75	31	absent	Trisomy 18	Omphalocele	Discharge
9	30	66	12	1,9	47,XYY	Omphalocele, lemon sign	IUEF, discharge
10	26	70	13	2,2	Turner S.	Cystic hygroma	IUEF, discharge
11	39	63	12	absent	Trisomy 21	Cystic hygroma, Echogenic bowel	IUEF, discharge
12	38	61	12	absent	Trisomy 21	Cystic hygroma	Discharge
13	29	60	12	absent	Trisomy 21	Cystic hygroma, Cardiac anomaly	Discharge
14	45	65	12	absent	Trisomy 21	Pelviectasis	Discharge
15	37	62	12	absent	Trisomy 21	None	Unknown
16	25	52	11	2,3	Turner S.	None	Live birth
17	29	64	12	1,5	Trisomy 21	None	Live birth
18	40	56	12	2,2	Turner S.	None	Unknown
19	25	52	11	2,3	47,XXY	None	Live birth

*mother's age, IUEF: intrauterine ex fetus, CRL: crown-rump length; NBL: nasal bone length.

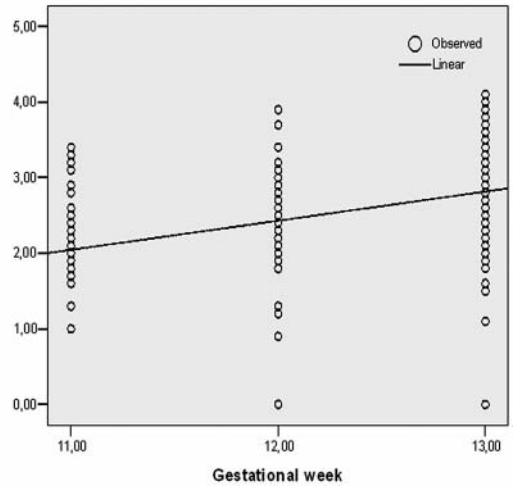

Figure 2. — Linear regression table regarding NBL and gestation week.

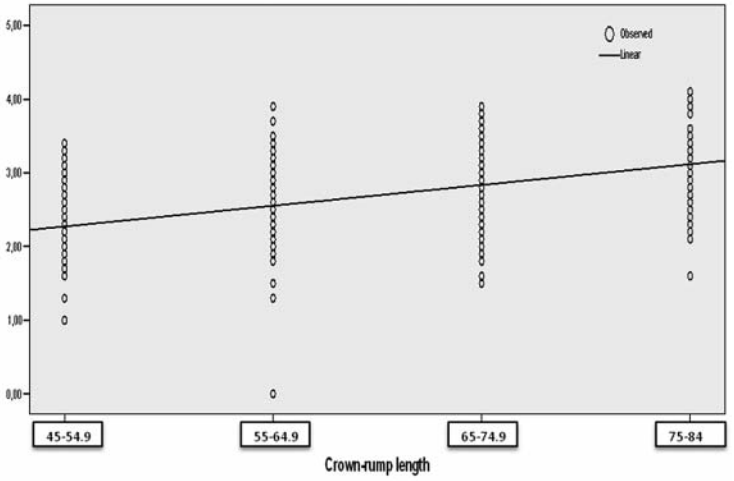

Figure 3. — Linear regression table regarding NBL and CRL

Discussion

Evaluation of the fetal NB is one of the most important components of first-trimester screening for chromosomal abnormalities. It has been suggested that absence or hypoplasia of the fetal NB is highly associated with trisomy 21 and other chromosomal abnormalities at 11^{+0}-13^{+6} weeks of gestation [1, 4-7]. Recent studies have shown that ethnicity is a significant determinant of fetal NB evaluation [8, 9]. Prefumo *et al.* [9] reported the largest series in the assessment of fetal NB in the first trimester, and demonstrated a significant difference in the rate of visualization of fetal NBs in mothers of different ethnic origins. Therefore, the normal reference values of the fetal NBL are of great importance for the definition of NB hypoplasia [1].

Normative data for the fetal NBL in the first trimester have been established in the Caucasian [13], African-American [8], Latin American [14], Chinese [15], and Korean populations [16]. In the Turkish population, Kelekci *et al.* [10], Sivri *et al.* [12], and Ozer *et al.* [11] studied fetal NBLs in different regions of Turkey. In the present study, the authors developed a nomogram by evaluating 479 healthy fetuses in the Eastern Black Sea region of

Table 5. — *Results of previous studies estimating reference values for fetal nasal bone length in various populations.*

Author	n	Place of study	11^{+0-6}							12^{+0-6}							13^{+0-6}						
			2.5%	5%	10%	50%	90%	95%	97.5%	2.5%	5%	10%	50%	90%	95%	97.5%	2.5%	5%	10%	50%	90%	95%	97.5%
Cicero *et al.*, 2002 (1)	500	UK					1.3							1.5							1.8		
Orlandi *et al.*, 2003 (5)	1027	Italy, Holland			2.0	2.5	3.2					2.1	2.7	3.3					2.2	2.9	3.5		
Sonek *et al.*, 2003 (13)	129	USA	1.3	1.4		2.3		3.3	3.4	1.7	1.8		2.8		4.2	4.3	2.2	2.3		3.1		4.6	4.8
Bekker *et al.*, 2004 (19)	90	Holland				2.3							2.6							2.9			
Chen *et al.*, 2006 (15)	2169	Chinese									1.7		2.2		2.8			2.0		2.5		3.2	
Moon *et al.*, 2006 (16)	827	Korean	1.2			1.5		1.9		1.4			1.7		2.1		1.6			1.9		2.3	
Casasbuenas *et al.*, 2009 (14)	1040	Chile	$1.0^{\neq}$	1.0		1.5		1.8	2.1^{μ}	$1.2^{\neq}$	1.2		1.7		2.2	2.4^{μ}	$1.4^{\neq}$	1.4		1.9		2.4	2.6^{μ}
Ozer *et al.*, 2010 (11)	415	Turkish		1.8		2.5		3.0			2.1		2.9		3.3			2.7		3.4		4.1	
Curent study	479	Turkish	1.3	1.4	1.4	2.2	3.1	3.3	3.4	1.6	1.8	1.9	2.5	3.3	3.4	3.6	2.2	2.3	2.4	2.9	4.0	4.1	4.2

$^{\neq}$ Marked values represent 3% ; $^{\mu}$ Marked values represent 97th percentile

Turkey. Mean NBL according to CRL was higher than those reported by Kelekci *et al.* [10] and Sivri *et al.* [12], but not that reported by Ozer *et al.* [11]; NBL according to CRL in the 50% percentile and NB length of 2.5 mm at the 11th week of gestation, 3.3 mm at the 12th week, and 3.4 mm at the 13th week. Our values for the same weeks were 2.2, 2.5 and 2.9 mm, respectively. Compared with those from other countries, the present results were similar to the mean NBL at 11^{+0} - 13^{+6} weeks gestation reported by Orlandi *et al.* [5] and Sonek *et al.* [13]. On the other hand, mean NBLs were significantly higher than those reported for the Korean and Latin American populations [14, 16] and slightly higher than that reported for the Chinese population [15].

NB hypoplasia or absence in the first trimester is an important clue in the early identification of chromosome abnormalities such as trisomy 21. Zoppi *et al.* [17], Cicero *et al.* [1], Otano *et al.* [7], Orlandi *et al.* [5], and Ozer *et al.*[11], reported NB absence in 70%, 69.9%, 66.7%, 60%, and 66.7%, respectively, of fetuses with Down syndrome, and 0.2%, 0.25%, 0.5%, 0,6%, and 1% of unaffected fetuses. However, Wong *et al.* [18] estimated the rate of absent NB slightly lower in both Chinese fetuses with aneuploidy (40.0%) and normal karyotype (0.88%). They also reported NB hypoplasia/absence in other chromosomal abnormalities as well as trisomy 21 [1, 5]. Cicero *et al.*[1] showed absence of NB in 57.1% of 18 cases with trisomia 21 in the first trimester and 8.8% of cases with Turner syndrome. In parallel with other studies, the present authors determined that NBL was not visible in one of 480 healthy fetuses (0.2%), six of nine fetuses (66.6%) with trisomy 21, and two of four fetuses (50%) with trisomy 18. Moreover, when the values below 2.5 standard deviation were taken into consideration, the NBs of two of nine fetuses (22.2%) with trisomy 21 were hypoplastic, while the NBL was at the lower limit of the normal range in one fetus with trisomy 21. However, in contrast to Cicero *et al.*[1] and Zoppi *et al.* [17], the present authors were unable to show NB hypoplasia or absence in Turner syndrome. This may be attributed to the low number of our Turner syndrome cases.

One limitation of this study was that it was hospital-based and the present is a tertiary hospital. Incidence of chromosomal anomaly and amniocentesis level was therefore very high as a result of all problematic gravidas being sent from surrounding hospitals.

The results of previous studies estimating reference values for fetal nasal bone length in various are summarized in Table 5 [1, 5, 11, 13-16, 19]. Examination of the fetal profile for the presence or absence of the NB during the first trimester of pregnancy provides substantial information on fetal chromosomal abnormalities. Absence or hypoplasia of the fetal NB is usually associated with fetal trisomies. Although measurement of the NB is not currently used as a routine screening tool in prenatal sonographic evaluation, it will take its place among the powerful sonographic markers of trisomy 21. However, in NB measurement ethnic and technical differences should be evaluated according to population-specific nomograms so that NB measurements can be accurately interpreted. The fact that the results of the present study are different from those of three studies [10-12] may support the present authors' idea. This data on NBL measurement may contribute national data for the development of a national nomogram for the Turkish population.

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Address reprint requests to:
S. GUVEN, M.D.
KTÜ Tıp Fakültesi, Farabi Hastanesi
Kadın Hastalıkları ve Doğum ABD,
61080 Trabzon (Turkey)
e-mail: drsuleymanguven@yahoo.com