Zeynep Kamil Med J 2022;53(4):207–212
DOI: 10.14744/zkmj.2022.24865

ORIGINAL ARTICLE

Reference ranges of nasal bone length, pre-nasal thickness, and pre-nasal thickness-to-nasal bone length ratio in low-risk pregnant women: A retrospective and cohort study from Türkiye

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ABSTRACT

Objective: The aim of this study was to determine the reference ranges of second trimester nasal bone length (NBL), pre-nasal thickness (PT), and PT/NBL ratios of low-risk pregnant women in Turkish population.

Material and Methods: Pregnant women of 16–28th gestational age who underwent ultrasonographic fetal screening between November 2021 and June 2022 were retrospectively analyzed. Fetuses with congenital malformations, high risk in antenatal screening tests, diagnosed with aneuploidy, and pregnant women of non-Turkish ethnic origin were excluded from the study. Fetuses were classified as ≤19^{+6} weeks, 20^{+0}–20^{+6} weeks, 21^{+0}–21^{+6} weeks, 22^{+0}–22^{+6} weeks, 23^{+0}–23^{+6} weeks, and ≥24^{+0} weeks. NBL, PT, and PT/NBL ratio was evaluated for each gestational age separately.

Results: A total of 242 fetuses were included in the study. The mean NBL and mean PT increased with gestational age (6.42±0.65 at 20^{+0}–20^{+6} weeks versus 7.65±0.79 at 23^{+0}–23^{+6} weeks and 3.10±0.62 at 20^{+0}–20^{+6} weeks vs. 3.55±0.63 at 23^{+0}–23^{+6} weeks, respectively). Both NBL and PT were positively correlated with gestational age whereas the PT/NBL ratio was constant throughout the second trimester (PCC=0.81, $p<0.001$, PCC=0.56, $p<0.001$, and PCC=−0.07, p=0.255, respectively). The mean PT/NBL ratio in the second trimester was calculated as 0.46 (95% CI, 0.45–0.47, 5th p=0.35 and 95th p=0.62).

Conclusion: The reference ranges for NBL, PT, and PT/NBL ratio may vary in different populations. Therefore, the use of population-specific nomograms may lead to higher success rates in Down syndrome screening.

Keywords: Down syndrome, nasal bone length, prenasal thickness, prenasal thickness-to-nasal bone length ratio, trisomy 21, ultrasound.

Cite this article as: Akalın M, Kara M, Akalın EE, Gök K, Kul G, Büyükbayrak EE. Reference ranges of nasal bone length, pre-nasal thickness, and pre-nasal thickness-to-nasal bone length ratio in low-risk pregnant women: A retrospective and cohort study from Türkiye. Zeynep Kamil Med J 2022;53(4):207–212.

Received: September 08, 2022 **Revised:** September 19, 2022 **Accepted:** September 26, 2022 **Online:** November 10, 2022
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Zeynep Kamil Medical Journal published by Kare Publishing. Zeynep Kamil Tıp Dergisi, Kare Yayıncılık tarafından basılmıştır.

INTRODUCTION

Down syndrome was first described in 1866 and is one of the most common aneuploidies in newborns.[1,2] The fact that Down syndrome is still the most common aneuploidy continues to increase researchers' interest in prenatal diagnosis of this syndrome. In recent years, Down syndrome screening has shifted to the first trimester and non-invasive prenatal testing is widely used. On the other hand, second trimester ultrasonographic findings in pregnant women who could not reach the first trimester screening tests remain important in the pre-natal diagnosis of Down syndrome, and these ultrasonographic findings may include the typical facial profile. The typical Down syndrome facial profile includes varying degrees of midface hypoplasia, absence or hypoplasia of the nasal bone, flat face, and subcutaneous skin edema.[3–5] Lymphatic system abnormalities and changes in genes controlling the α1 and α2 chains of type VI collagen on chromosome 21 cause varying degrees of skin edema and increased skin thickness in certain areas such as the face and neck.[5,6] Both increased skin thickness and typical facial appearance in Down syndrome have led researchers to identify fetal facial sonomarkers in the prenatal diagnosis of this syndrome. Nasal bone length (NBL), pre-nasal thickness (PT), frontomaxillary facial angle, and prefrontal space ratio are among these facial sonomarkers, and these sonomarkers can be quantified by measuring them as fetal profile parameters.[7–10]

It was first suggested in 1995 that NBL could be a second trimester ultrasonographic marker in Down syndrome, and subsequent reports supported this finding.[7,11,12] Then, in 2005, Maymon et al.[8] suggested that PT and PT/NBL ratio could be used as a new second trimester ultrasonographic marker in Down syndrome. In subsequent studies, the PT/NBL ratio was reported to be the most effective facial sonomarker for Down syndrome screening in the second trimester, with a detection rate of 86–100%.[3,4,13,14] On the other hand, the normal ranges of these ultrasonographic markers may differ between races and ethnicities. A study of Chinese women reported 46% of lower detection rate for the PT/NBL ratio in Down syndrome screening.[15] In another recent Asian study, the authors suggested that NBL, PT, and the PT/NBL ratio have high performance in detecting Down syndrome, but reference ranges for these markers should be established based on individual populations.[3]

The aim of this study was to determine the reference ranges of NBL, PT, and PT/NBL ratios for Down syndrome screening in second trimester ultrasonography of low-risk pregnant women in our population.

MATERIAL AND METHODS

In this study, pregnant women of 16–28th gestational age who underwent ultrasonographic fetal scanning between November 2021 and June 2022 in a tertiary center perinatology department were retrospectively analyzed. The study was approved by the ethics committee of our university and was conducted in accordance with the principles of the Declaration of Helsinki. A single physician (M.A.) performed all measurements. All fetuses whose NBL and PT were measured in fetal ultrasonographic scanning were included into the study. Fetuses with congenital malformations, high risk in antenatal screening tests (first trimester combined test, second trimester

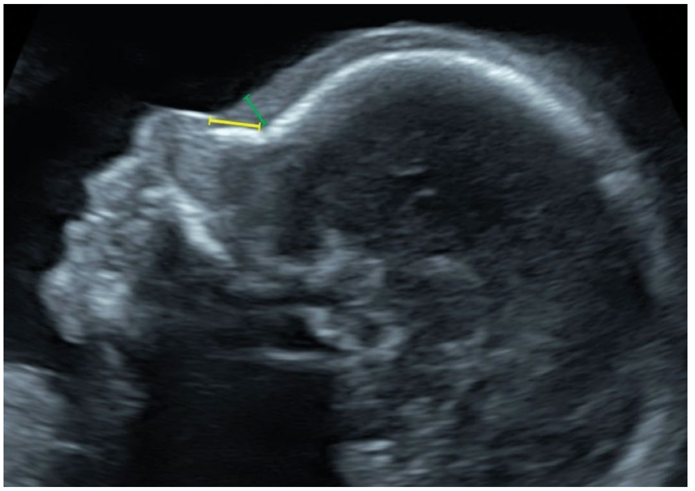

Figure 1: Ultrasonographic image of NBL and PT measurement in the second trimester Yellow line indicates NBL, green line indicates PT.

NBL: Nasal bone length; PT: Pre-nasal thickness.

triple or quadruple serum screening test and non-invasive prenatal screening test), diagnosed with aneuploidy in the pre-natal or post-natal period, and pregnant women of non-Turkish ethnic origin were excluded from the study.

Maternal age, obstetric history, pre-natal and post-natal follow-up data, and fetal ultrasonography reports of the patients were obtained from the electronic data system of our hospital. Second trimester fetal ultrasonographic scanning and fetal echocardiography were performed on all fetuses included in the study according to published guidelines.[16,17] The gestational ages of the fetuses were confirmed according to the crown rump length measurement in the first trimester ultrasonography. Gestational age was determined according to maternal last menstrual period in fetuses without first trimester crown rump length measurement. The mean fetal biometric age was defined as the age of fetus calculated by the ultrasonography device software using biparietal diameter, abdominal circumference, and femur length measurements. Fetuses were classified as ≤19^{+6} weeks, 20^{+0}–20^{+6} weeks, 21^{+0}–21^{+6} weeks, 22^{+0}–22^{+6} weeks, 23^{+0}–23^{+6} weeks, and ≥24^{+0} weeks according to their gestational ages. NBL, PT, and PT/NBL ratio was evaluated for each gestational age separately.

NBL and PT Measurements

GE Voluson E6 (GE Medical Systems, Milwaukee, USA) ultrasonography device with a 4–8 Mhz transabdominal probe was used for the measurements. NBL and PT measurements were performed according to the criteria described by Maymon et al.[8] Two-dimensional fetal profile images were obtained in midsagittal section to measure PT and NBL. In the midsagittal section, an image including the nasal bone, lips, corpus callosum, diencephalon, and maxilla as a single line without the zygomatic bone was obtained. Care was taken to maintain an insonation angle close to 45° or 135° for measurements. To perform the measurements, images of the fetal profile were enlarged to fill the entire screen. NBL was measured from the base of the nose to the distal end of the white ossification line. PT was measured as the shortest perpendicular distance from the junction of the

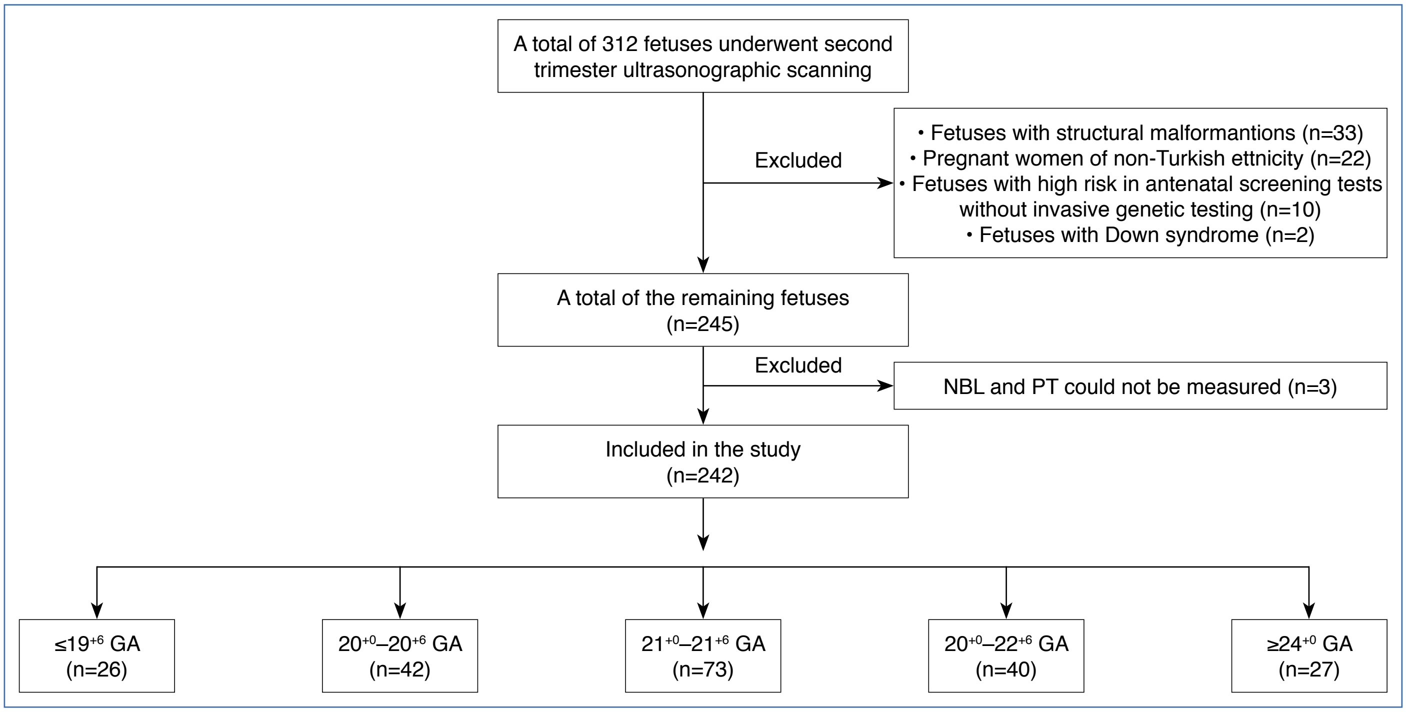

Figure 2: The flowchart of the fetuses included in the study.

frontal bone and the lower end of the nasal bone to the outer surface of the skin (Fig. 1). Hypoplastic nasal bone was determined as <5th percentile for gestational age.[18]

Statistical Analysis

SPSS software version 21 (IBM, US) package program was used for statistical analysis. Descriptive data were expressed as numbers (%) and mean±standard deviation. The 5th, 50th, and 95th percentiles of NBL, PT, and PT/NBL ratios for each gestational age were calculated with a 95% confidence interval. Distributions of NBL, PT and PT/NBL ratio according to gestational age were visualized using graphics. The correlation coefficients of NBL and PT with gestational age were calculated using the Pearson correlation test. The distribution of continuous data was tested using the Kolmogorov–Smirnov test. The Mann–Whitney U test was used to compare the values of two independent groups.

RESULTS

A total of 312 fetuses underwent second trimester ultrasonographic scanning during the study period. The flow chart of the fetuses included in the study is shown in Figure 2. Thirty-three (10.6%) fetuses with structural malformations (13 (4.2%) fetuses with congenital heart defects, 9 (2.9%) fetuses with central nervous system anomalies, 2 (0.6%) fetuses with skeletal dysplasia, 2 (0.6%) fetuses with pes equinovarus, 2 (0.6%) fetuses with cystic hygroma, 2 (0.6%) fetuses with hydrops fetalis, 1 (0.3%) fetus with pulmonary sequestration, 1 (0.3%) fetus with cleft lip and palate anomaly, and 1 (0.3%) fetus with congenital diaphragmatic hernia), 22 (7.1%) pregnant women of non-Turkish ethnicity, 10 (3.2%) fetuses with high risk in antenatal screening tests without invasive genetic testing, and 2 (0.6%) fetuses with

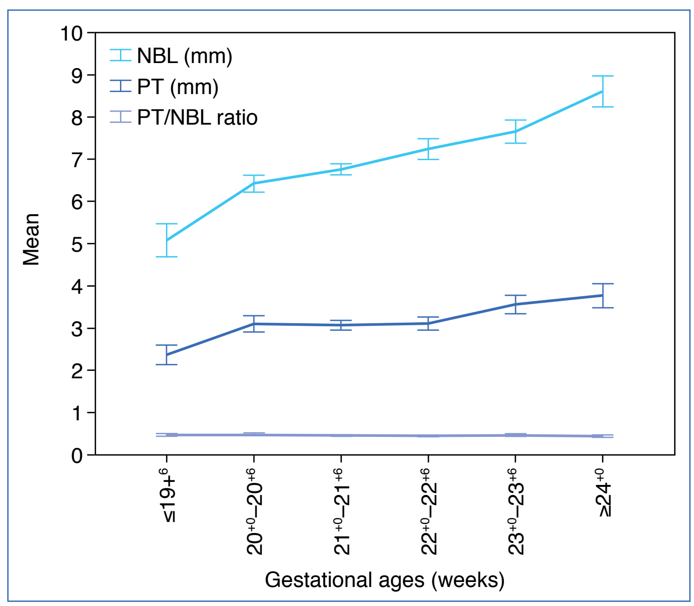

Figure 3: Mean values of NBL, PT, and PT/NBL ratio according to gestational age in the second trimester.

NBL: Nasal bone length; PT: Pre-nasal thickness.

Down syndrome were excluded from the study. NBL and PT could be measured appropriately in 242 (98.8%) of the remaining 245 fetuses, and a total of 242 fetuses were included in the study. Nine (3.7%) of the pregnancies included in the study were multiple pregnancies (6 (2.5%) twin pregnancies and 3 (1.2%) triplet pregnancies). The mean age of the pregnant women was 28.9±5.6 years, the mean gravida was 2.4±1.3, the mean parity was 1.0±1.1, and the mean history of miscarriage in the previous pregnancy was 0.4±0.6.

Table 1: The mean NBL of the fetuses and the 5th, 50th, and 95th percentiles of the NBL according to the gestational age

Gestational age (weeks)	n	Mean±SD	95% CI		Percentiles		
			Lower	Upper	5th	50th	95th
≤19+6	26	5.07±0.99	4.67	5.47	3.14	4.95	7.18
20+0–20+6	42	6.42±0.65	6.22	6.62	5.50	6.25	7.59
21+0–21+6	73	6.76±0.56	6.63	6.89	6.07	6.70	7.96
22+0–22+6	40	7.24±0.76	6.99	7.48	5.52	7.10	8.40
23+0–23+6	34	7.65±0.79	7.37	7.92	6.40	7.50	9.27
≥24+0	27	8.61±0.93	8.23	8.97	7.04	8.90	10.08

Values are stated as number and mean±standard deviation; NBL: Nasal bone length; CI: Confidence interval; SD: Standard deviation.

Table 2: The mean PT of the fetuses and the 5th, 50th, and 95th percentiles of the PT according to the gestational age

Gestational age (weeks)	n	Mean±SD	95% CI		Percentiles		
			Lower	Upper	5th	50th	95th
≤19+6	26	2.36±0.58	2.13	2.59	1.45	2.40	3.46
20+0–20+6	42	3.10±0.62	2.90	3.29	2.60	2.90	3.80
21+0–21+6	73	3.06±0.52	2.94	3.19	2.30	2.90	4.19
22+0–22+6	40	3.11±0.49	2.95	3.26	2.40	3.10	3.99
23+0–23+6	34	3.55±0.63	3.34	3.77	2.57	3.55	4.83
≥24+0	27	3.77±0.72	3.48	4.05	2.58	3.60	5.16

Values are stated as number and mean±standard deviation; PT: Pre-nasal thickness; CI: Confidence interval; SD: Standard deviation.

Table 3: The mean PT/NBL ratios of the fetuses and the 5th, 50th, and 95th percentiles of the PT/NBL ratios according to the gestational age

Gestational age (weeks)	n	Mean±SD	95% CI		Percentiles		
			Lower	Upper	5th	50th	95th
≤19+6	26	2.36±0.58	2.13	2.59	1.45	2.40	3.46
20+0–20+6	42	3.10±0.62	2.90	3.29	2.60	2.90	3.80
21+0–21+6	73	3.06±0.52	2.94	3.19	2.30	2.90	4.19
22+0–22+6	40	3.11±0.49	2.95	3.26	2.40	3.10	3.99
23+0–23+6	34	3.55±0.63	3.34	3.77	2.57	3.55	4.83
≥24+0	27	3.77±0.72	3.48	4.05	2.58	3.60	5.16

Values are stated as number and mean±standard deviation; PT: Pre-nasal thickness; CI: Confidence interval; SD: Standard deviation.

The mean gestational age at the time of ultrasonography was 21.7±2.1 weeks and the mean fetal biometric age was 21.8±2.1 weeks. The mean NBL, mean PT, and mean PT/NBL ratio of the fetuses and the 5th, 50th, and 95th percentiles of the NBL, PT, and PT/NBL ratio with 95% confidence interval according to the gestational age are shown in Tables 1, 2 and 3. There was a positive correlation between gestational age and both NBL and PT measurements (PCC=0.81, p<0.001 and PCC=0.56, p<0.001, respectively) (Fig.

3). In addition, there was a positive correlation between NBL and PT measurements (PCC=0.57, p<0.001). On the other hand, the PT/NBL ratio was not correlated with gestational age and was constant throughout the second trimester (PCC=−0.07, p=0.255) (Fig. 3). Since PT/NBL is constant at all gestational ages, the mean PT/NBL ratio in the second trimester was calculated as 0.46 (95% CI, 0.45–0.47, 5th p=0.35 and 95th p=0.62).

In only 1 (0.4%) of 242 fetuses, the PT/NBL ratio was above 0.8, which was defined as the cutoff value for predicting Down syndrome in the previous studies.[4,14] This fetus had an increase in PT without nasal bone hypoplasia. On the other hand, nasal bone hypoplasia was detected in 2.1% (n=5) of fetuses. While one of the fetuses with Down syndrome had a cystic hygroma, the other fetus did not have any structural malformations. The mean PT/NBL ratios of fetuses with nasal bone hypoplasia were significantly higher than those without nasal bone hypoplasia, but there was no significant difference between the mean PT (0.57±0.07 vs. 0.45±0.08, p=0.003 and 2.84±0.48 vs. 3.15±0.68, p=0.178, respectively). The PT/NBL ratios of two fetuses with Down syndrome were 0.89 and 0.92. While one of these two fetuses with Down syndrome had nasal bone hypoplasia, the NBL of the other fetus was normal for gestational age.

DISCUSSION

This study provides a comprehensive evaluation of the normal ranges of second trimester NBL, PT, and PT/NBL ratios in low-risk pregnant women in the Turkish population. NBL and PT measurements are not difficult to perform, and several studies have found that ultrasonographic images on which these measurements performed are easy to obtain and have good repeatability of the measurements.[3,19,20] The fact that appropriate NBL and PT measurements were made in more than 98% of fetuses in our study shows that these measurements can be easily perform in routine second trimester ultrasonographic screening. Although NBL measurement alone can be used as an ultrasonographic marker of Down syndrome, it may be practical to measure PT and NBL together, given that PT is measured on the same ultrasonographic image. Our results showed that NBL and PT increased in relation to gestational age, while the PT/NBL ratio remained constant throughout the second trimester. This finding was similar to the results of the previous studies conducted in the European population.[4,14] On the other hand, in an Asian study, the PT/NBL ratio increased gradually during the second trimester.[3] Moreover, the threshold values for NBL, PT, and PT/NBL ratio in both the European and Asian population were different from those in our study. These findings supported the fact that population-specific threshold values should be used for the normal range of NBL, PT, and PT/NBL ratio in euploid fetuses.

In a well-designed previous study from Türkiye involving 650 euploid fetuses, nomograms of NBL, PT, and PT/NBL ratios in the second trimester were reported.[5] In this study, mean NBL values according to gestational age were similar to the mean NBL in our study. However, in this study, NBL increased in relation to gestational age, while the 5th percentile values of NBL decreased between 20 and 23 weeks of gestation (5,7 mm at 20–21 weeks and 4,6 mm at 22–23 weeks). In this study, similar to our results, PT increased with gestational age. However, contrary to our results, the mean PT/NBL ratio was higher and the PT/NBL ratio slightly decreased with gestational age (0.55 at 20–21 weeks and 0.50 mm at 23–24 weeks). The reason for this difference is that there was a positive correlation between NBL and PT measurements in our study; therefore, the PT/NBL ratio remained constant with increasing gestational age. In addition, non-Turkish pregnant women were not excluded in this study, and therefore, pregnant women with different ethnic origins may have caused a slight difference in the NBL and PT measurements. Therefore, we suggest that our results may be more accurate for nomograms in the Turkish population.

In the previous studies, it has been proposed that the increased PT/NBL ratio is a sonomarker for Down syndrome in the second trimester.[3,4,8,13,14] However, the threshold values and detection rates of the PT/NBL ratio were different in these studies. In the study of De Jong-Pleij et al.,[14] when the 95th percentile (>0.8) of the PT/NBL ratio was used as a cutoff value, the detection and false positive rates for Down syndrome were 100% (95% CI, 89–100) and 5% (95% CI, 2–11), respectively. However, only 30 fetuses with Down syndrome were included in this study. In a subsequent study involving 145 fetuses with Down syndrome, the detection rate for a cutoff value of PT/NBL ratio >0.8 (95th percentile) was 86.2% (95% CI, 79.3–91.2) with 5% (95% CI, 1.7–11.3) false positives rates.[4] In a recent Asian study involving 340 euploid and 11 Down syndrome fetuses, the 95th percentile of the PT/NBL ratio for gestational age ranged from 0.56 to 0.68, and the increased PT/NBL ratio had 100% sensitivity and 92% specificity.[3] In our study, the PT/NBL ratio in both fetuses with Down syndrome was above the 95th percentile. On the other hand, only one of these two fetuses had hypoplastic nasal bone; therefore, if only nasal bone hypoplasia was considered as a facial sonomarker, the other fetus would be considered normal. Although this finding provides a prediction that the PT/NBL ratio may be a more sensitive sonomarker than nasal bone hypoplasia, further analysis could not be performed because only two fetuses with Down syndrome were found in our study. Nevertheless, we suggest that the PT/NBL ratio is a very useful sonomarker, considering these high success rates in detecting Down syndrome and the constant PT/NBL ratio throughout the second trimester in our population. Therefore, we believe that invasive genetic diagnostic testing should be offered to parents as an option in cases with increased PT/NBL ratio in second trimester ultrasonography.

An increased PT and/or PT/NBL ratio can be used as an ultrasonographic sonomarker to screen for Down syndrome in first trimester ultrasonography. In a retrospective study involving 44 fetuses with Down syndrome, the PT/NBL ratio was found to be significantly higher in fetuses with Down syndrome compared to normal fetuses.[21] In this study, the PT/NBL ratio (at a cutoff value of 0.8) had a sensitivity of 86.4% and a specificity of 98.4% for Down syndrome screening. In addition, similar to the second trimester, the PT/NBL ratio was not altered by gestational age. The authors of the study suggested that the PT/NBL ratio was superior to the isolated contribution of NBL and PT measurements in first trimester Down syndrome screening.

The present study had some limitations. Although we included only low-risk pregnant women in our study, karyotype analyzes, and microarray analyzes for possible submicroscopic rearrangements were not performed in all fetuses. On the other hand, it would be difficult to design a study in which genetic analyzes are performed on all fetuses at low risk for chromosomal abnormalities. Another limitation of the study due to its retrospective nature is that it could not evaluate the intraobserver and interobserver variability. The strengths of the study were that the study was conducted in a tertiary center and the measurements were performed by an experienced physician with a high-resolution ultrasonography device.

CONCLUSION

NBL and PT can be easily measured in routine second trimester ultrasonographic screening. The normal ranges for NBL, PT, and PT/NBL ratio may vary in different populations. Therefore, the use of population-specific nomograms for these measurements may lead to higher success rates in Down syndrome screening. In Turkish pregnant women, while NBL and PT increase in correlation with gestational age, the PT/NBL ratio remains constant throughout the second trimester. Considering the high detection rate of PT/NBL ratio in Down syndrome screening, using this ratio in the second trimester may provide convenience to physicians. The studies with larger numbers of cases are needed to evaluate the performance of the PT/NBL ratio in Down syndrome screening in the Turkish population.

Statement

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 02.09.2022, number: 09.2022.1137).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MA; Design – MA; Supervision – EEB; Resource – MA; Materials – GK; Data Collection and/or Processing – MK; Analysis and/or Interpretation – KG; Literature Search – EEA; Writing – MA; Critical Reviews – EEB.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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