

Reference values of nuchal fold thickness in an Iranian population sample

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Background: Considering that ethnicity and gestational age (GA) could affect the value of nuchal fold thickness (NFT) in mid-trimester, we aimed to determine the reference intervals of NFT values for each gestational week from 16 to 24 weeks of pregnancy among a group of Iranian pregnant women. **Materials and Methods:** In this cross-sectional study, medical files of pregnant women who underwent fetal anomaly scanning at 16–24 weeks of gestation were reviewed and the following data were extracted: GA, value of NFT, value of nuchal translucency (NT) in their previous ultrasound study, if available, and head circumference (HC). The 5th, 25th, 50th, 75th, and 95th percentiles of NFT for each gestational week were determined. The association between NFT and HC, GA, and NT were also determined. **Results:** Medical files of 882 pregnant women were studied. The expected 95th percentile value of NFT between 16th and 24th weeks of gestation ranged from 4 mm to 5.9 mm. The mean (standard deviation) of NFT increased with GA from 2.67 (0.90) mm at 16th weeks to 4.69 (0.71) mm at 24th weeks. There was a significant positive association between NFT and GA ($\beta = 1.11, P < 0.001$), HC ($\beta = 0.21, P < 0.001$), and NT ($\beta = 0.351, P < 0.001$). **Conclusion:** The findings of this study revealed that before the 20th week of gestation, the appropriate cutoff value of NFT is 5 mm, and for 21st to 24th weeks, the proper cutoff is 6 mm. However, for providing more conclusive results, further studies with larger sample size and considering the impact of other influencing variables are recommended.

Key words: Nuchal fold, pregnancy trimester, prenatal diagnosis, second, ultrasonography

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INTRODUCTION

Ultrasonic measurements have become a standard practice in prenatal screening for chromosomal abnormalities worldwide.^[1] Different ultrasonographic markers have been introduced and evaluated in this field for the first and second trimesters. One of the most important markers of the second trimester with appropriate sensitivity and specificity is nuchal fold thickness (NFT) which was first introduced in 1985 by Benacerraf *et al.*^[2-5] According to the findings of different studies, the sensitivity and false positive rate for the marker were 75% (average of 34%) and 0.5% (ranging from 0% to 3%), respectively.^[5-7]

The association of NFT with an increased risk of fetal aneuploidy has been reported previously.^[8]

The results of a meta-analysis on the utility of different second-trimester markers for Down syndrome indicated that increased NFT is associated with increased risk of the syndrome with a likelihood ratio of 19.18.^[9]

In addition, the performance of NFT in the prediction of some fetal aneuploidies including trisomies 21, 18, and 13 during early second trimester has been reported in previous studies.^[10,11]

Evidence indicated that the value of NFT could be influenced by some maternal, fetal, and technical factors such as gestational age (GA), fetal gender, presence or absence of nuchal cord, fetal presentation, cephalic index, and imaging technique.^[12-15]

Although several studies showed that an NFT of ≥ 6 mm is the accepted cutoff for the detection of trisomy 21,

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some studies recommended that for improving the outcome of prenatal screening and increasing the sensitivity of the test, it is better to decrease the cutoff of NFT to 5 mm.^[16-18] However, there are still controversies in this field. Some studies suggest that proving population-based cutoffs for each gestational week would be a more accurate screening tool for chromosomal abnormalities than using the NFT ≥ 6 mm cutoff for all GAs.^[19]

Given that ethnicity and GA could affect the value of NFT in mid-trimester and providing proper screening cutoffs level would be useful in better diagnosis of fetal aneuploidies, we aimed to determine the reference intervals of NFT values for each gestational week from 16 to 24 weeks of pregnancy among a group of Iranian pregnant women.

MATERIALS AND METHODS

This study was conducted as a cross-sectional study, during a 5-year period (2011–2016). All pregnant women who underwent fetal anomaly scanning at 16–24 weeks' gestation in a private ultrasonography center in Isfahan, Iran, were included.

The protocol of the study was approved by the Institutional Review Board and the Regional Ethics Committee of Isfahan University of Medical Sciences with a research project number of 395703.

The records of pregnant women with the following ultrasonographic findings were not included: any fetal abnormalities, multiple pregnancies, fetal hydrops, or intrauterine fetal demise.

The records of pregnant women with incomplete or missing data were excluded from the study.

Medical files of the selected women were reviewed and the following data were extracted: GA, value of NFT, head circumference (HC), and value of nuchal translucency (NT) in their previous first-trimester ultrasound if available.

The 5th, 25th, 50th, 75th, and 95th percentiles of NFT for each gestational week were determined. The association between NFT and HC, NT, and GA were also determined.

Ultrasonographic measurements

All ultrasonographic measurements were performed by an expert radiologist (AA) during 16–24th weeks of gestation.

Methods of NT measurement were described in detail in previous research.^[20] It was measured based on the recommended criteria by the Fetal Medicine Foundation.^[21]

Fetal NFT measurements were performed by transabdominal ultrasonography using GE Voluson 730 Pro, Expert (GE Healthcare, Milwaukee, WI) with a multifrequency: 3.5–5 MHz curvilinear transducer. NFT measurement was performed according to the previously described standard protocol.^[22,23]

A transcerebellar plane of the fetal head displaying the cavum septum pellucidum, atria of the lateral ventricles, cerebral peduncles, and cerebellar hemispheres was visualized. NFT was measured by placing the calipers from the outer edge of the occipital bone to the outer edge of the overlying skin.

NFT was measured at least two times and the images were reviewed to select the most appropriate image and increase the accuracy of NFT measurement. The maximum value of NFT was considered as the final record of the marker.

Statistical analysis

Recorded quantitative data were reported as mean (standard deviation) analyzed using SPSS ver. 21 software (SPSS Inc., Chicago, IL, USA). Different percentiles of thickness including 5th, 25th, 50th, 75th, and 95th percentile in different gestational weeks (16–24th weeks) were computed. Repeated measures ANOVA was used for comparing the mean values of NFT over the time. The association between NFT and HC, NT, and GA was determined using simple regression, and the results were reported as a regression coefficient along with 95% confidence interval (95% CI) for the coefficient.

RESULTS

In this study, medical files of 882 pregnant women were selected and studied. The 5th, 25th, 50th, 75th, and 95th percentile values of NFT according to GA are presented in Table 1. *Post hoc* test indicated that the mean of NFT was not different between 16th and 17th weeks, 19th and

Table 1: The mean (standard deviation) and expected 5th, 25th, 50th, 75th, and 95th percentile values of nuchal fold thickness (mm) in each gestational week

Gestational age (week)	Patients (n)	Mean (SD)	NFT				
			5 th	25 th	50 th	75 th	95 th
16	49	2.67 (0.90)	1.8	2.05	2.5	3.0	4.8
17	236	2.80 (0.69)	1.7	2.3	2.8	3.2	4.0
18	322	3.27 (0.86)	2.0	2.7	3.2	3.8	4.9
19	156	3.60 (0.89)	2.2	3.0	3.5	4.2	5.0
20	80	3.69 (0.67)	2.6	3.2	3.7	4.2	5.0
21	43	4.06 (0.81)	2.7	3.5	4.0	4.5	5.5
22	21	4.21 (0.95)	2.3	3.5	4.2	5.0	5.9
23	16	4.38 (0.83)	2.6	3.9	4.4	5.0	5.0
24	12	4.69 (0.71)	3.1	4.3	4.9	5.2	5.2

SD=Standard deviation; NFT=Nuchal fold thickness

20th weeks, 21st and 22nd weeks, 21st and 23rd weeks, 22nd and 23rd weeks, 22nd and 24th weeks, and 23rd and 24th weeks.

The mean NFT value in each gestational week along with the 5th and 95th percentiles is shown in Figure 1.

Simple linear regression analysis indicated that there was a significant positive association between NFT and GA ($\beta = 1.11$, $P < 0.001$, 95% CI: 0.968–1.254) and HC ($\beta = 0.21$, $P < 0.001$, 95% CI: 0.18–0.23).

In 380 cases, both NT and NFT were measured. There was a positive association between NFT and NT ($\beta = 0.351$, $P < 0.001$, 95% CI: 0.085–0.617).

DISCUSSION

In this study, we determined the normal reference interval of NFT among a sample of Iranian pregnant women during 16–24 weeks of gestation. Our findings indicated that the mean NFT level increased by GA ranging from 2.67 to 4.69. The 95th percentile value of NFT in the 16–20th weeks of gestation was ≤ 5 and after that had an increasing trend, but still was < 6 .

As mentioned, the most accepted NFT cutoff for predicting Down syndrome is 6 mm. Some studies suggested that decreasing the cutoff to 5 mm would increase the sensitivity of the marker for the detection of chromosomal abnormalities. In accordance with increasing sensitivity, the approach would also increase the rate of false positivity which is not favorable for an appropriate screening test. So that, some studies recommended to use population-based cutoff for each gestational week in this field.^[16-19]

Goynumner *et al.* in Turkey have determined the cutoff values of NFT based on GW among 2313 singleton pregnancies between 15th and 24th GW. They found a positive correlation between GA and NFT. According to their results, the 95th percentile values of NFT during 15–24th GW were as follows: 4.7, 4.77, 5.0, 5.5, 5.76, 5.9, 6.0, 6.1, 6.5, and 6.8 mm. They concluded that using the single cutoff of 6 mm would not be appropriate for the evaluation of chromosomal abnormalities during the 2nd trimester of pregnancy and have a false positive rate of 1.8%–37%. Moreover, they

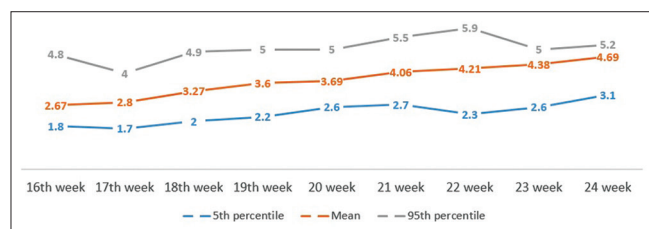


Figure 1: The mean nuchal fold thickness (mm) value in each gestational week along with the 5th and 95th percentiles

recommended to determine the NFT cutoff values for each GW by population-based percentiles.^[19]

Manotaya *et al.* for the first time in Thailand have determined the nomogram of NFT in Thai pregnant women during 14–17 weeks of pregnancy. They showed that the mean value of NFT increased steadily by increasing GA from 2.59 mm to 4.12 mm.^[24]

In another recent study, in Brazil, the normal reference interval of NFT among 2559 normal singleton pregnancies between 18 and 24 weeks of pregnancy was determined and the association between NFT and GA was evaluated. They indicated that the mean fetal NFT ranged from 3.98 mm to 4.83 mm during the studied GA and showed a significant correlation between NFT and GA.^[25]

Singh and Biswas in Singapore have reported the GA-specific NFT values between 16 and 24 weeks of gestation. Similar to all mentioned studies, they also reported an increasing mean value for NFT from 16th to 24th weeks of gestation (3.13–5.08 mm). They reported that the 95th percentile value of NFT at 24th weeks was < 6 mm and considered the threshold of 6 mm for NFT for GA of 20–24 weeks.^[26]

The results of our study regarding the association between NFT and GA were similar to the above-mentioned studies. The mean range of NFT in our population was not similar to the studies which could be explained by the role of ethnicity. Considering that the 95th percentile of NFT measurements from 16 to 20 weeks were ≤ 5 mm and after that were < 6 mm, it seems that for GA of 16–20 weeks, the threshold would be decreased to 5 mm.

For more accurate conclusion in this field and preventing overestimation of NFT, inappropriate invasive testing and putting a pregnancy at the risk of miscarriage using biochemical screening factors and planning a prospective study for evaluation of the sensitivity and rate of false positivity would be helpful.

NT is the only sonographic screening marker for trisomy 21, with reported 80% sensitivity and 5% false positive rate.^[27,28] Some previous studies have evaluated the association between NT and NFT. Although it is suggested that the pathophysiology of both ultrasonographic markers is similar, studies in this field did not find any correlation between them.^[29-31] In this study, we found a significant association between NF and NT, which indicated that the markers could not be used as independent factors for the detection of fetal aneuploidy.

Three studies did not find any correlation between the markers and concluded that they may be used as independent markers for screening of chromosomal abnormalities.^[29-31]

Maymon *et al.* showed a small correlation between NT and NF, but they also recommended to use the markers independently for evaluation of Down syndrome risk.^[30]

Salomon *et al.* also did not report a significant association between NT measured at 11–14 weeks of gestation and NFT at 20–24 weeks of gestation. They concluded that the markers provide an independent contribution in prenatal screening of trisomy 21.^[31]

Migueluez *et al.* have reported a significant correlation between NT and NFT. They indicated that in cases with increased NT in the first trimester, the frequency of cases with NFT values more than 97.5th percentile is higher than those with normal NT level. They concluded that using the findings, we could provide a multivariate risk model using both markers for better screening of fetal aneuploidy.^[32] Our findings in this field could also be useful for constructing mentioned multivariate risk model including both first- and second-trimester ultrasonographic markers.

The limitations of our study were small sample size and the retrospective design of the study. In addition, it is recommended to evaluate the influence of other variables such as fetal gender, presentation, cephalic index, and the presence or absence of nuchal cord on NFT values for obtaining more accurate results.

The strength of the current study was that it was the first study among Iranian pregnant women in this field.

CONCLUSION

The findings of this study demonstrated that before the 20th week of gestation, the appropriate cutoff value of NFT is >5 mm and for 21–24th weeks the proper cutoff is >6 mm. However, for providing more conclusive results, further studies with larger sample size and considering the impact of other influencing variables are recommended.

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Conflicts of interest

There are no conflicts of interest.

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