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Research Article
Subclinical Hypothyroidism Effect on Interpretation of Nuchal Translucency Early in Pregnancy

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Abstract

Background and Objective: Subclinical and overt hypothyroidism represent major health problems with an increasing prevalence and a potential serious impact on mother health. It affects the measurement of nuchal translucency to the degree that forced the obstetricians to re-evaluate it as a single screening test for aneuploidies and encouraged them toward the use of other maternal serum markers early in pregnancy. To clarify the effect of subclinical hypothyroidism on the interpretation of nuchal Translucency in early pregnancy. **Materials and Methods:** A prospective comparative case control study was conducted at the out patients clinic of the Obstetrical Department at Al-Yarmouk Teaching Hospital from the 1st of September 2016 to the 1st of September 2018. About 140 pregnant women were enrolled in the study; 100 of them were apparently healthy pregnant women in their first trimester (11-13^{+6} weeks) assigned as a control group and the other 40 were pregnant women of the same gestational age diagnosed as having subclinical hypothyroidism after thyroid function screening of 500 pregnant women who attended this tertiary hospital and were assigned as patient group. Ultrasound measurement of the crown ramp length and nuchal translucency had been done for all participants. The data from both groups were statistically analyzed and compared. **Results:** Forty patients had subclinical hypothyroidism from a total of 500 women screened (8%). The mean measurement of nuchal translucency was significantly higher in the patient group compared to control group (2.92±0.96 versus 2.45±0.62 mm, respectively) and there was a significant positive linear correlation between nuchal translucency (NT) and thyroid stimulating hormone (TSH) level. All those with abnormally raised nuchal translucency delivered healthy fetuses. **Conclusion:** Subclinical hypothyroidism might affect the interpretation of nuchal translucency and reduce its significance as a screening test in that population.

Key words: Subclinical hypothyroidism, nuchal translucency, pregnant women, thyroid function gestational age

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hypothyroidism is common in reproductive age group women as it affects around 1% of pregnant women worldwide[1], its prevalence during pregnancy varies from about 2% in the west to more than 10% in India and it is significantly higher in Asian countries compared with the west[2-5]. Subclinical hypothyroidism(SH) with an elevated TSH and normal Free thyroxin FT4 level affects about 2.5% of pregnant women[6]. Owing to the similarities between the symptoms of pregnancy and thyroid disease, delayed diagnosis is expected with the possibilities of adverse effects on pregnancy outcome, therefore women diagnosed with hypothyroidism should continue thyroid replacement therapy during pregnancy and biochemical euthyroidism is the aim as corrected thyroid disease does not appear to affect pregnancy outcome[1]. However, poorly controlled disease is associated with a variety of complications of which is the congenital malformation[7] which is the core of this work as it studied nuchal translucency (NT) as an early screening test for these abnormalities in those women with subclinical hypothyroidism to determine its reliability in those population. The fetal NT is unique among other ultrasound markers in that it has become a component of aneuploidy screening offered to all women. As an isolated marker, NT detects 64-70% of fetuses with Down syndrome at a false positive rate of 5%[8]. Even in those fetuses who born normally, a reduced intelligence and motor development with a neuro developmental delay had been found in some studies[9]. Given the concerns about the fetal effects of maternal subclinical hypothyroidism, current advice from the British Endocrine Society is that women with hypothyroidism should be given thyroxine replacement at a dose that ensures their thyroid function tests are normal, with free T4 at the upper end of the normal range and TSH at 2.5 mU L^{-1} or less[10]. Due to lack of proper screening program of this important health problem so the present study was aimed to examine the effect of subclinical hypothyroidism on nuchal translucency in early pregnancy.

Patients and method: This prospective comparative case-control study was conducted at the outpatients clinic of Obstetrics and Gynecology Department at AL Yarmouk Teaching Hospital from the 1st of September, 2016 to the 1st of September, 2018. This hospital is a tertiary referral hospital in Baghdad which receives more than 3500 pregnant women per year. The protocol of the study had been approved by the local ethical research committee of Obstetrics and Gynecology.

One hundred forty pregnant women aged 18-40 years were enrolled in the current study after obtaining an informed verbal consent. Forty were those pregnant women diagnosed as having subclinical hypothyroidism with an elevated TSH level but normal T4 after screening of a total of 560 women in early pregnancy for thyroid function and assigned as a patient group while the control group were 100 women who were apparently healthy pregnant women and matched for age, gestational age and parity.

A detailed history was taken from all participants and the inclusion criteria were:

- Singleton pregnancy
- 10-13 weeks and 6 days gestation
- 18-40 years old

While the exclusion criteria were:

- Medical diseases as diabetes or hypertension
- Current pregnancy complications as hyperemesis gravidarum, infections and threatened miscarriage
- Personal or family history of chromosomal abnormalities as Down syndrome

Gestational age was calculated from the last menstrual period of a reliable and regular cycle and confirmed by an early pregnancy ultrasound report. Complete physical examination was done for all women. Detailed ultrasound by the same ultra-sonographer, using GE voluson E6 Mashine that was equipped with transabdominal volumetric probe, was done for all participants including confirmation of viability, crown-rump length (CRL) and measurement of nuchal translucency. For the measurement of NT: The gestational age was between 11-13 weeks and 6 days, the CRL was between 45 and 84 mm, a mid-sagittal view of the face which occupies with the chest full screen, the fetus was in a neutral position, the widest part of translucency was measured as shown in Fig. 1 and 2. During the scan more than one measurement were taken and the maximum one that meets all the above criteria was recorded [11].

Blood sample (5 cc) was obtained by the standard venipuncture technique. The samples were centrifuged and stored at -80°C. All samples were sent to the laboratory to assess thyroid function test by enzyme-linked immunosorbent assay (ELISA).

This study followed those women with abnormal NT through their pregnancy by monthly antenatal visits to the date of parturition.

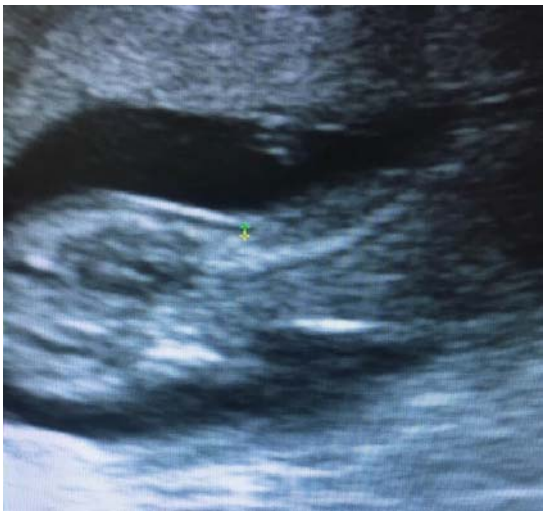

Fig. 1: Measurement of NT<3.5 mm (normal)

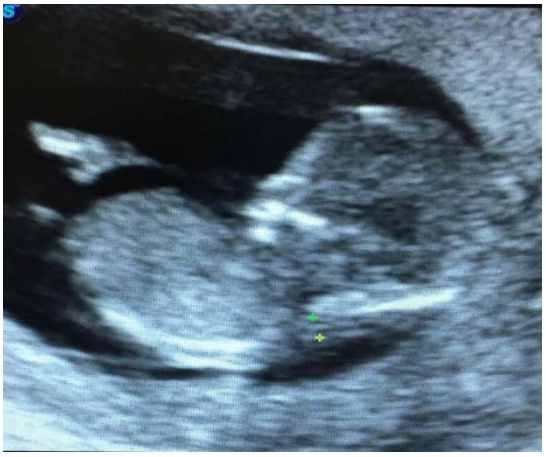

Fig. 2: Measurement of NT >3.5mm (abnormal)

Statistical analysis: The Statistical Package for Social Sciences (SPSS) version 24 was used to analyze the study data which was presented as mean with standard deviation (SD) and median with range. Student t-test (two tailed) was used to compare the demographic data between the patients and control groups. Mann-Whitney U non-parametric test was used to compare the thyroid function parameters and nuchal translucency values between the patients and control groups.

The correlation between NT measurements and TSH values was evaluated according to Spearman's correlation. p-value was considered significant if less than 0.05.

RESULTS

Forty patients had subclinical hypothyroidism from a total of 500 women screened (8%). The demographic and biochemical variables are shown in Table 1 which revealed that there were no significant differences between the patients and control groups regarding age, gestational age and parity as p-values were 0.82, 0.67 and 0.22 respectively while the BMI was significantly higher in the patients group as p-value was 0.008. The mean TSH level was significantly higher in the patients group 6.69 MIU L^{-1} compared to 2.27 MIU L^{-1} for the control group as the p-value was less than 0.05 while the free T4 level was comparable between the two groups with no significant difference.

The nuchal translucency was measured for both groups and the results of comparison were shown in Table 2 which revealed that its mean was significantly higher in those diagnosed with subclinical hypothyroidism compared to those with normal thyroid function (2.92±0.96 vs.

Table 1: Comparison of demographic and biochemical variables between the two groups

Parameters	Patient (No. = 40)	Control (No. = 100)	p-value
Age (years)			
Mean±SD	27.5±6.6	27.8±6.4	0.82
Median (range)	26 (21-33.2)	25 (21-35)	
Gestational age (weeks)			
Mean±SD	12.03±0.85	12.2±0.8	0.67
Median (range)	12 (11-13.5)	12 (11.4-13.2)	
Parity			
Mean±SD	1.36±0.8	2.4±1.8	0.22
Median (range)	1 (0.5-2.2)	2 (1.5 – 4.3)	
BMI (kg m^{-2})			
Mean±SD	23.1±1.54	22.34±1.92	0.008
Median (range)	21.02 (19.3-25)	20.4 (19-22.3)	
TSH(MIU\L)			
Mean±SD	6.69±2.04	2.27±1.05	0.0001
Median(range)	6.41 (4.52-9.64)	2.49 (1.48-3.56)	
Free T4 (µg dL^{-1})			
Mean±SD	7.31±2.2	7.34±2.03	0.37

Table 2: Comparison of nuchal translucency measurements for both groups

	Patient		Control		
Nuchal translucency(mm)	No.	Percentage	No.	Percentage	p-value
0.5-1.5	7	17.5	11	11	< 0.001
1.6-2.5	9	22.5	39	39	
2.6-3.5	11	27.5	48	48	
3.6-4.5	13	32.5	2	2	
Mean±SD	2.92±0.96		2.45±0.62		
Median (range)	1.61 (0.52-3.64)		1.49 (0.48-3.09)		

Table 3: Correlation between NT and TSH

Spearman's rho	NT	TSH
NT		
Correlation coefficient	1.000	0.204**
Sig. (2-tailed)	0.0	0.006
N	180	180
TSH		
Correlation coefficient	0.204**	1.000
Sig. (2-tailed)	0.006	0.0
N	180	180

**Correlation is significant at the 0.01 level (2-tailed), NT: Nuchal translucency. TSH: Thyroid stimulating hormone

2.45±0.62 mm) as the p-value is less than 0.05 and 13 patients (32.5%) had abnormally high NT measurement (>3.5 mm) compared to 2 only (2%) in the control group.

From this study there was a positive linear correlation between NT measurements and TSH values (r = + 0.204) which was significant at 0.01 level according to Spearman's correlation as shown in Table 3.

This study followed those patients with abnormal NT (15 patients) till delivery and all of them delivered a normal looking fetuses.

DISCUSSION

To date, unfortunately there is a lot of debate about the significance of early pregnancy screening tests in the presence of medical problems specially thyroid diseases. Nuchal translucency represents a major radiological screening marker that can be influenced by different factors [12]. Women with hypothyroidism treated with levothyroxine should meet the increased demand of thyroxin early in pregnancy otherwise they might have major fetal adverse effects, 30-50% of women may be inadequately managed during this critical time of the fetal life [13].

The current study focused on the effects of subclinical hypothyroidism on the NT measurement. Both groups were matched for age, parity and weeks of gestation to reduce the effects of these variables on NT measurement. Hantoushzadeh *et al.*[12] found a significant correlation between these factors and NT measurement. BMI is significantly higher in the patient group and this finding is comparable to the findings of Rotondi *et al.*[14] and Sanyal *et al.*[15], who concluded that subclinical hypothyroidism affects thermogenesis and body energy expenditure when the level of TSH is significantly higher than the normal range. The TSH level was significantly higher in the patient group compared to the control group while the free T4 level was comparable for all participants in this study, those patients with subclinical hypothyroidism have no or little symptoms with great similarity to the symptoms of the pregnancy and a wide range of adverse pregnancy outcomes to the mother and the fetus that mandates laboratory screening early in pregnancy[16,17].

In the current study there was a significant difference in NT between the study groups with the mean of measurement was higher in the patient group than control. Actually; studies about this subject were very limited Socolov *et al.*[18] found that hypothyroidism might influence the NT independently and they found a positive association between T4 and NT but not with TSH which was different from the findings in the current study that showed a significant positive linear correlation between TSH and NT. All these findings might be explained by the effect of thyroid disease on the fetal tissue with the resultant increase in NT due to tissue edema with fluid collection. Dhaifalah *et al.*[19] adviced the incorporation of thyroid markers in Down syndrome screening as these increased the sensitivity and detection rate of these tests inspite of great awareness of obstetricians to the major adverse effects of subclinical hypothyroidism on the pregnant women and their fetuses, a large number of patients are still ignoring the importance of this common problem and its management early in pregnancy with the resultant delay in optimizing their thyroid function leading to possible neuro-developmental disorders in the newborns[12,20,21].

Unfortunately universal screening for thyroid problem is not recommended till now and the measurement of thyroid hormones early in pregnancy typically preformed only in those patients at risk of hypothyroidism or known to have thyroid problem before the pregnancy, this creates a big dilemma in the early detection and management of SH[21]. Subclinical hypothyroidism increases NT measurement which represents a powerful marker for aneuploidies in modern obstetrics but

its measurement requires skills and professional practice in radiology in addition to its affection by many factors which reduce its significance and therefore this highlights the way towards the importance of its combination with other maternal serum markers to minimize this problem[20,22].

CONCLUSION

- Subclinical hypothyroidism increases the measurement of NT and reduces its significance as a screening test for chromosomal abnormalities. This mandates combination of NT with other maternal serum markers as a screening test in SH
- There was a significant positive linear correlation between TSH and NT measurements
- Further studies with a larger sample size and different population to establish a higher threshold for normal measurement in cases of SH

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