Trimester-specific thyroid hormone changes in normal pregnant Egyptian women

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Introduction
The range of normal thyroid functions during pregnancy differs between ethnic groups. Establishment of trimester- and assay-specific reference intervals for every population is recommended.
Aim
Assessement of the changes in thyroid function tests across the different trimesters in normal pregnant Egyptian females.
Subjects and methods
The study included 150 normal pregnant Egyptian females, recruited from Cairo university hospital antenatal care clinic, with 100 age-matched non-pregnant females, as a control group. Serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) were measured in the three trimesters of pregnancy for every patient. Thyroid peroxidase antibodies (TPO Abs) were also assessed.
Our study showed that TSH reference ranges, using the 2.5th and the 97th percentiles, were 0.6–4.3, 0.9-3.7 and 1.0–4.2 mIU/ml for the first, second and third trimesters respectively. The median TSH concentration (50th percentile) was lower in the first trimester (2.1 mIU/ml) in comparison with the second and third trimesters of (2.6 and 2.9 mIU/ml respectively). FT4 reference ranges, using 2.5th to 97th percentile, were 0.9–2 and 0.7–1.4 and 0.6–1.2 ng/dl for the first, second and third trimesters respectively. The median FT4 concentration was higher in the first trimester (1.5 ng/dl) in comparison with the second and third trimesters of (1.1 and 1.0 ng/dl respectively). The percentage of positive TPO Ab was higher in pregnant women than that of age matched non-pregnant ladies (15.3 vs 2%, $P<0.001$).
Conclusion
Our study established trimester-specific changes in thyroid hormone reference ranges in normal pregnant Egyptian females. A larger population-based study would help to confirm those ranges.

Keywords:
pregnancy, thyroid functions, thyroid peroxidase antibodies, thyroid-stimulating hormone

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Introduction

Pregnancy is associated with significant hormonal changes and metabolic demands resulting in altered thyroid function. Thyroid dysfunction, in particular hypothyroidism, can affect the health of both the mother and the fetus during pregnancy [1]. Thyroid disorders are commonly present in pregnancy and puerperium. Early and appropriate detection of thyroid dysfunction and timely interventions improve maternal-fetal prognosis, so application of reliable gestational-specific reference values for determining thyroid disorders in pregnant women would be a necessity [2].

Interpretation of thyroid function tests in pregnancy can be difficult due to physiological changes, which include: first, decreased thyroid-stimulating hormone (TSH) level during the first trimester due to the stimulatory effect of human chorionic gonadotropin; second, increased degradation of thyroid hormones thyroxin (T4) and triiodothyronine (T3) by placental type 3 deiodinases; third, increased thyroid-binding globulin due to estradiol and altered hepatic glycosylation decreasing its clearance; fourth, increased urinary iodide excretion; and fifth, alterations in the immune system, leading to amelioration of an underlying autoimmune thyroid disease [3].

Ethnic differences in the level of thyroid hormones exist among individuals probably because of the differences in genetic susceptibility caused by polymorphisms or differences in environmental exposures [4].

Consequently, the American Thyroid Association, the Endocrine Society and the European Endocrine Society and other major professional organizations recommend the use of trimester-specific and assay-specific reference ranges for maternal serum TSH and FT4 [5].

Participants and methods

The study included 150 normal Egyptian women in the first trimester of pregnancy (mean age was 26±6 years) recruited from Kasr Al-Ainy Hospital Outpatient Antenatal Care Clinic, and 100 age-matched nonpregnant women as a control group. (confirmed by normal beta human chorionic gonadotropin). Both the study and the control group subjects were on iodine sufficient-diet. Women with twin pregnancy or history of thyroid disease with or without treatment, thyroidectomy, malignancy, neck surgery/irradiation, history of liver or kidney diseases or diabetes mellitus, history of amiodarone or lithium therapy, or recent administration of iodinated radiologic contrast were excluded. The study was approved by Cairo University Ethics Committee and Review Board. All participants provided written informed consents.

The study population was subjected to: thorough history and clinical examination. Obstetric history was taken; gestational age was calculated from the first day of the last normal menstrual period, and gestational age less than 14, 14–27, and greater than 28 weeks comprised the first, second, and third trimesters of pregnancy, respectively. Assessment of BMI for each one was calculated using the formulaweight/height^2. All participants were clinically euthyroid. Serum samples were taken in the three trimesters for assessment of TSH and FT4 by ELISA kit (using the quantitative sandwich immunoassay technique). Thyroid peroxidase antibodies (TPO Ab) level was measured by ELISA reader (ORGENTEC Diagnostika GmbH, Germany).

Statistical analysis was performed using SPSS, Version 25. χ^2-Test was used to compare between the groups with respect to categorical data. Comparisons between two groups for normally distributed numeric variables were done using the Student *t*-test while for non-normally distributed numerical variables, comparisons were done by Mann–Whitney *U*-test. Comparisons between more than two groups were performed by the analysis of variance for normally distributed and Friedman test for non-normally distributed variables. Pearson's correlation coefficients were used to measure the strength of association between the normally distributed measurements. Spearman's correlation coefficient was calculated for nonnormally distributed variables. Logistic regression analysis was done to give adjusted odds ratio and magnitude of the effect of different risk factors. *P* value less than or equal to 05 was considered significant.

Results

The median TSH concentrations of pregnant women was statistically lower than that of nonpregnant women (2.0 vs 3.2 mIU/l, $P<0.001$). The median FT4 concentrations of pregnant women was higher than that of nonpregnant women (1.5 vs 1.3 ng/dl, $P<0.001$). The percentage of positive TPO Ab was higher in pregnant women than that of age-matched nonpregnant women (15.3 vs 2%, $P<0.001$). Median TPO Ab titre was higher in pregnant women (20 mIU/ml) than that of the control (20 vs 8 mIU/ml, $P<0.005$). Median TSH concentration at first trimester (2 mIU/l) was statistically lower than that of second (2.6 mIU/l) and third (2.9 mIU/l) trimesters ($P<0.001$). TSH ranged from 0.3 to 4.3, 0.9 to 4.7, and 1.0 to 4.9 mIU/l during the first, second, and third trimesters, respectively. Median FT4 concentration of pregnant women at first trimester (1.5 ng/dl) was statistically higher than that of second (1.1 ng/dl) and third (1.0 ng/dl) ($P<0.001$) trimesters. FT4 reference range is 0.8–2, 0.6–1.7, and 0.5–1.5 ng/dl during the first, second, and third trimesters, respectively. The median range of TSH in TPO-Ab-positive pregnant women was higher than TSH median range in TPO-Ab-negative pregnant women in different trimesters (P=0.002, 0.002, and 0.003 in the first, second, and third trimesters, respectively). No significant correlation was found between TPO-Ab titre and TSH level (P=0.092), but there was a

Table 1 Comparison between thyroid functions and thyroid peroxidase antibodies in pregnant women (first trimester) and healthy control subjects

Factors	Pregnant		Controls		*P* value
	Mean±SD	Median (range)	Mean±SD	Median (range)	
FT4	1.4±0.3	1.5 (0.8–2)	1.3±0.3	1.3 (0.8–1.9)	<0.001
TSH	1.9±0.8	2 (0.3–4.3)	3.3±0.8	3.2 (1.6–4.9)	<0.001
TPO-Ab	23±11	20 (9–59)	18±6	18 (7–40)	0.005

FT4, free thyroxine; TPO Ab, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone. $P<0.05$ is considered significant.

Table 2 Comparison of thyroid-stimulating hormone and free thyroxine concentrations in the three trimesters

Factors	First trimester median (range)	Second trimester median (range)	Third trimester median (range)	*P* value
TSH	2.1 (0.3–4.3)	2.6 (0.9–4.7)	2.9 (1–4.9)	<0.001
FT4	1.5 (0.8–2)	1.1 (0.6–1.7)	1 (0.5–1.5)	<0.001

FT4, free thyroxine; TSH, thyroid-stimulating hormone. $P<0.05$ is considered significant.

Table 3 Trimester-specific percentile values for thyroid-stimulating hormone and free thyroxine

Factors	First trimester			Second trimester			third trimester			*P* value
	2.5th percentile	50th percentile	97th percentile	2.5th percentile	50th percentile	97th percentile	2.5th percentile	50th percentile	97th percentile	
TSH	0.6	2.1	4.3	0.9	2.6	3.7	1	2.9	4.2	<0.001
FT4	0.9	1.5	2	0.7	1.1	1.4	0.6	1	1.2	<0.001

FT4, free thyroxine; TSH, thyroid-stimulating hormone. $P<0.05$ is considered significant.

significant negative correlation between TPO-Ab titre and FT4 level in pregnant women (P=0.034). The results of the study are summarized in Tables 1–3.

Discussion

In this study, we demonstrate the changes in thyroid function and trimester-specific maternal FT4 and TSH concentrations in pregnant Egyptian population; we also report the prevalence of positive thyroid autoimmunity in otherwise euthyroid women in our population. Differences in free thyroid hormones due to different analytical methods have been reported in pregnancy. There is also considerable population-dependent differences in FT4 and TSH reference intervals using the same analytical method [6]. Several studies have demonstrated that there is a significant ethnic and geographic variation in TSH levels in pregnancy and cast doubt on the validity of the upper limit of 2.5 mIU/l. For that reason, current guidelines advocate the use of population-based, and assay-specific trimester ranges for thyroid function tests [7,8].

Analysis of our data showed that median TSH concentrations of Egyptian pregnant women in the first trimester is statistically lower than that of nonpregnant women. TSH values were lowest in the first trimester group and increased in the second and third trimesters, respectively, while FT4 levels showed the opposite trend.

Regarding TSH reference ranges across the three trimesters of pregnancy, this current study shows that TSH reference range, using the 2.5th and the 97th percentiles, is 0.6–4.3, 0.9–3.7, and 1–4.2 mIU/ml for the first, second, and third trimesters, respectively. And the median (50th percentile) is 2.1, 2.6, and 2.9 mIU/ml for the first, second, and third trimesters, respectively.

TSH upper reference limit during the first trimester, mentioned by this present study, approximates to the upper reference range reported by Li *et al.* [9] in their studies conducted on pregnant Chinese women using the medians and the 2.5th and 97.5th percentiles for TSH and FT_4 analyses. The reference interval levels of TSH during the first trimester were 0.14–4.87 mIU/l and that it decreased significantly from the seventh week of gestation, being at 4–6 weeks of gestation and at 7–12 weeks of gestation, 0.56–5.31 and 0.10–4.34 mIU/l, respectively.

The TSH reference intervals mentioned by this present study also approximate to a study done by Moon *et al.* [8], on 465 Korean pregnant women. The TSH reference intervals using the 2.5th and 97.5th percentiles were 0.01–4.10, 0.01–4.26, and 0.15–4.57 mIU/l for the first, second, and third trimester, respectively. And from the first trimester to the third trimester, the median TSH levels showed a significantly increasing trend ($P<0.0001$) and FT4 reference intervals were 0.83–1.65, 0.71–1.22, and 0.65–1.13 ng/dl for the first, second, and third trimester, respectively, showing a significantly decreasing trend ($P<0.0001$), which is in agreement with the findings mentioned in this study.

TSH upper limits reported during pregnancy in this study were lower than those observed in a previous study conducted on Indian populations where the first trimester TSH ranges was 0.44–5.78 mIU/l [10].

We found also significant variations when we compared our results with those reported in different populations such as a study done in USA where the upper limit of TSH in the first trimester was only 1.06 mIU/l [11] and with a study done on Sweden pregnant women which reported a TSH

reference range of 0.24–2.99, 0.46–2.95, and 0.43–2.78 mIU/ml for the first, second, and third trimesters, respectively [12].

This study showed that the percentage of positive TPO antibodies was statistically higher in pregnant women (15.3%) than that of age-matched non-pregnant women (2%). In a similar study by Negro *et al.* [13], the overall prevalence was found to be 11.7%, while it was 12.5% in a study by Olivieri *et al.* [14] and 11% in a study done by Meena *et al.* [15].

TSH levels were significantly higher and FT4 was significantly lower in TPO Ab positive euthyroid women as compared with TPO Ab negative women in the present study. This rise in TSH levels in euthyroid TPO Ab positive women could be due to autoimmune-mediated inflammation of the thyroid gland that leads to a decline in the functional reserve of the thyroid gland and reduced adaptation of thyroid gland to the physiological changes of pregnancy [16]. Similar results were observed by Prummel and Wiersinga [17]. Prospective studies by Glinoer *et al.* [18] in 1994 and Negro *et al.* [13] 12 years later found a progressive increase in TSH levels with progression of gestation in TPOAb euthyroid women. Therefore, both guidelines recommend that euthyroid women (not receiving LT4) who are positive for TPOAb require monitoring for hypothyroidism during pregnancy. On the other hand, Stagnaro-Green *et al.* [19] did not detect any significant difference between TSH levels and FT4 levels in between TPO Ab-positive and TPO Ab-negative euthyroid women. Lack of iodine status evaluation and the small sample size are important limitations of our study. A larger population-based study would help to confirm trimester-specific reference ranges for thyroid hormone levels during pregnancy. Multicenter collaborative study on the national level would help to confirm trimester-specific reference ranges for thyroid hormone levels during pregnancy and to ensure the inclusion of adequate numbers.

Conclusion

In conclusion, our study established trimester-specific changes in thyroid hormone reference ranges in normal pregnant Egyptian women. The difference in results between our study and other similar research works could be explained by different ethnic backgrounds.

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Conflicts of interest
There are no conflicts of interest.

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