

Reference Intervals in Thyroid Function Tests in the Third Trimester in Pregnant Filipino Women

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Abstract

Background: Pregnancy has been associated with differences in thyroid function.¹ Maternal thyroid dysfunction has been shown to be associated with fetal and obstetric complications and prompt management is of importance. It has thus been recommended by the British and American Thyroid Association^{11,12} that trimester-specific thyroid function test reference ranges be used in the assessment of thyroid dysfunction.

Normative values across the trimesters of pregnancy have been conducted in several countries^{13,17,19} and in the Philippines. Reference ranges in the first and second trimesters of pregnancy were conducted by Patal and Hamin et al. which showed values of TSH 0.14-3.84 uIU/mL, FT4 10.44-21.58 pmol/L, FT3 2.4-5.82 pmol/L in the first trimester and TSH 0.10-4.30 uIU/mL, FT4 9.10-19.40 pmol/L, FT3 2.70-5.190 pmol/L in the second trimester, respectively.

Objective: To establish third trimester reference intervals for free thyroid hormones (free triiodothyronine [FT3], free thyroxine [FT4]) and thyrotropin (TSH) from thyroid peroxidase antibody (TPOAb)-negative Filipino pregnant women.

Design: This is a prospective, cross-sectional study which included consecutive 200 healthy third-trimester

pregnant Filipino women attending Philippine General Hospital (PGH) out-patient services. Serum TSH, FT4, FT3, and TPOAb were measured.

Main outcome measures: Reference intervals are based on 2.5th and 97.5th percentiles for TSH, FT4, and FT3 among TPOAb-negative third-trimester pregnant Filipino patients.

Analysis: All numerical data were entered in MS Excel and analyzed using STATA 12. FT3, FT4 and TSH were expressed as mean \pm SD, range at 2.5th to 97.5th percentiles.

Results: The reference ranges for TSH, FT4 and FT3 in TPOAb-negative third-trimester pregnant population are as follows: TSH= 0.2-3.0 uIU/mL; FT4 = 9.16-18.64 pmol/L and FT3= 2.09-3.7 pmol/L.

Conclusion: Reference ranges for thyroid function tests for the third trimester of TPOAb-negative pregnant Filipino women were determined in this study and are as follows: TSH= 0.2-3.0uIU/mL; FT4 = 9.16-18.64pmol/L and FT3= 2.09-3.7pmol/L.

Keywords: pregnant, thyroid function test, third trimester, Filipino

Background

Pregnancy has been associated with differences in thyroid function compared to a non-pregnant state. Advances in the study of thyroid hormone physiology showed several trimester-specific changes in thyroid hormones such as (1) decreased thyroid stimulating hormone (TSH) during the first trimester due to stimulatory effect of human chorionic gonadotropin (hCG) which has a structural similarity with TSH; (2) increased thyroid-binding globulin (TBG)

due to estradiol and altered hepatic glycosylation decreasing its clearance; (3) increased urinary iodide excretion, which can cause impaired thyroid hormone production in areas of marginal iodine sufficiency; and (4) alterations in the immune system, leading to onset, exacerbation, or amelioration of an underlying autoimmune thyroid disease.¹ Moreover, this change in iodine status defines a difference in the thyroidal function and volume. Areas with restricted iodine intake exhibit greater thyroid volume increase and TSH levels exhibit a much greater increase in pregnancy.¹ The Philippines is classified as having an inadequate iodine intake with a mildly deficient iodine status as reported in the Iodine Status Worldwide: WHO Global Database on Iodine Deficiency in 2004² including an 88.1% of the pregnant population as having mildly deficient iodine status as reported in the Food and Nutrition Research Institute (FNRI) Iodine Nutriture Report of 2008.³

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Maternal thyroid dysfunction during pregnancy has been associated with different obstetric complications such as fetal deaths,⁴ placental abruption⁵ and gestational hypertension.⁵ Moreover, thyroid dysfunction is also associated with adverse neurodevelopmental outcomes in the offspring.^{7,8,9,10} Thus, identification of thyroid dysfunction in pregnancy and their subsequent management is of importance.

Due to these different factors affecting thyroid function, it has thus been recommended by the British Thyroid Association¹¹ and the American Thyroid Association¹² that trimester-specific thyroid function test reference ranges be used in the assessment of thyroid function tests in pregnant women.

Normative values specific to the laboratory assays used across the three trimesters of pregnancy have been conducted in iodine sufficient area (Sweden),¹⁹ in newly-iodine sufficient area (India)¹⁷ and iodine insufficient area (China).¹³ Other countries which have normative values for trimester-specific thyroid function tests include Malaysia,¹⁴ Spain,^{15,16} and Switzerland¹⁸. In the Philippines, reference ranges for TSH, FT4 and FT3 in TPOAb-negative in the first and second trimesters of pregnancy were conducted by Patal et al. and Hamin et al. which showed values of TSH 0.14-3.84uIU/mL, FT4 10.44-21.58 pmol/L, FT3 2.4-5.82 pmol/L in the first trimester²⁰ and TSH 0.10-4.30uIU/mL, FT4 9.10-19.40pmol/L, FT3 2.70-5.19pmol/L in the second trimester.

Significance

To our knowledge, there is no local data on normal trimester-specific thyroid function test in the Philippines. The Philippines, having an inadequate iodine intake with a mildly deficient iodine status,^{2,3} could possibly exhibit a different degree of thyroid function change compared with other iodine sufficient areas, thus needing a trimester-specific, laboratory assay specific normative thyroid function test values.

The previous studies done by Patal, et al. and Hamin, et al. in the reference interval in the thyroid function test in pregnant Filipino women involves first and second trimester data only. This study serves to complete the trimester-specific thyroid function test values in TPOAb-negative Filipino pregnant women and will serve as the first trimester-specific thyroid function test reference intervals done in the Philippines.

Objectives

To establish third trimester reference intervals for free thyroid hormones (FT3 and FT4) and TSH from TPOAb-negative Filipino pregnant women

Materials and Methods

Study Type:

Cross-sectional study

Study Population

Two hundred healthy adult pregnant women on their third trimester consulting at the Obstetrics and Gynecology Department out-patient services of the Philippine General Hospital (PGH) were recruited, particularly on their 28th to 42nd weeks age of gestation, assessed through their subject's last normal menstrual period and/or early ultrasound. Their medical history were taken to ascertain any chronic illness, thyroid illness in the past or present, medications (current and past) and family history of thyroid illness and obstetric history were reviewed. Excluded were women with goiter, history of hyperthyroid or hypothyroid disease, postpartum thyroiditis or thyroid surgery, signs or symptoms suggestive of thyroid hyperfunction or hypofunction, family history of goiter, hyperemesis gravidarum, trophoblastic disease, preeclampsia, presence of autoimmune disease (SLE, T1DM, etc), previous therapeutic head or neck irradiation, history of miscarriage or preterm delivery, thyroid antibodies (when known) and those in labor.

Physical examinations were done by the primary investigators to ascertain absence of goiter and signs of thyroid hypofunction or hyperfunction.

Sample Size Calculation

The minimum sample size requirement is measured using PASS (Power Analysis and Sample Size) software. A sample size of 126 was computed using a two-sided confidence interval of 95% with a 0.10 distance from the mean using a standard deviation of 0.565 taken from the studies of Patal, et al. and Jamin, et al. derived from the study of Panesar in China.¹³ Taking into consideration the probability of non-response, an increase by 20% would result in a minimum sample size of 152.

Description of Study Procedure

Informed consents were obtained from all of the subjects and blood extraction were carried out on the same day by the investigators to obtain a 5.0 ml whole blood sample which were run for FT4, FT3 and TPOAb using radioimmunoassay (RIA) method while TSH was measured using immunoradiometric assay (IRMA). FT4, FT3 and TSH on the 2.5th to 97.5th percentile of TPOAb-negative subjects were considered normative value for the third trimester.

Data Analysis

All numerical data were entered in MS Excel and analyzed using STATA 12. FT3, FT4 and TSH

were expressed as mean ±SD, range at 2.5th to 97.5th percentiles. Comparisons among different trimesters were performed using ANOVA.

Outcome Measure

Reference interval for thyroid function tests of TSH, FT4 and FT3 among TPOAb-negative third trimester pregnant Filipino women

Ethical Considerations

The study protocol was technically and ethically reviewed, and approved by the Technical Review Board of the Department of Medicine, PGH and by the University of the Philippines-Manila, Research Ethics Board (UPMREB).

Indemnification Policy

The subjects’ inclusion in this study is voluntary and no monetary or material compensation was used. Denial of inclusion did not result in denial of any medical service to the patient.

The study was safe and no complications were encountered during the process.

Results

General characteristics

Two hundred (200) healthy pregnant patients were recruited from PGH Obstetrics outpatient clinic from April 2013 to August 2013. Mean age was 27.5 ± 6.01 years old (mean ± SD). Majority of them are on their first pregnancy (38%) 31.5% on their second pregnancy, 14.5% on their third pregnancy, 11.5% on their fourth pregnancy and the remaining 4.5% are on their fifth or more pregnancy.

Of these 200 subjects, three were TPOAb positive (1.5%), and 197 (98.5%) were TPO negative. The reference values of the thyroid function test among the TPOAb-positive and TPOAb-negative pregnant women in the third trimester is shown in Table I.

Relationship of Thyroid Function Test with Age of Gestation

There is a significant correlation between AOG

and TSH levels as seen by the p value of 0.0075 (p value less than 0.05). The positive r value indicates positive correlation although a value of 0.1885 shows negligible correlation between the AOG and TSH (Figure 1).

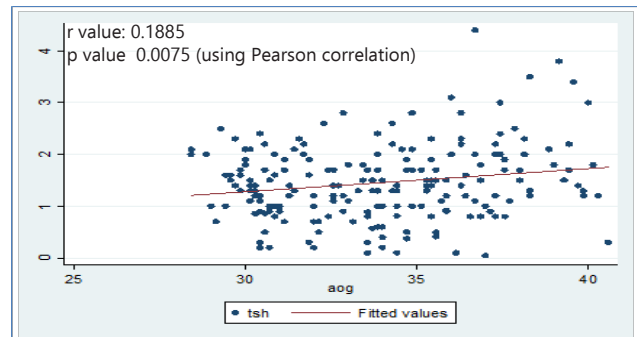


Figure 1: Thyrotropin scatter plot with fitted values

There is a significant correlation between AOG and FT4 levels as seen by the p value of 0.0037 (p value less than 0.05). The positive r value indicates weak positive correlation between the two such that as AOG increases, the level of FT4 also increases (Figure 2).

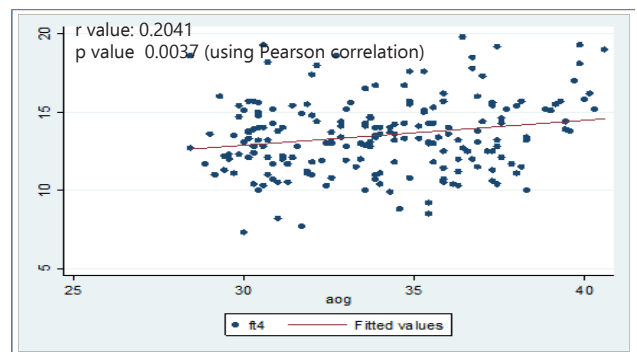


Figure 2: Free thyroxine scatter plot with fitted values

There is a non-significant correlation between AOG and FT3 levels as shown by the p value of 0.4197 (Figure 3).

Table I: Thyroid function test during third trimester (Mean, SD, 2.5th and 97.5th percentile)

Test	All (N=200)		TPOAb positive(N=3)		TPOAb negative(N=197)		P value
	2.5th-97.5th Percentile	Mean ±SD	2.5th-97.5th Percentile	Mean ±SD	2.5th-97.5th Percentile	Mean ±SD	
TSH (0.3-3.8uIU/mL)	0.2-3.00	1.46 ±0.72	1.06-3.72	2.33 ±1.40	0.2-3.0	1.44 ±0.70	0.0323*
FT4 (11.0-24.0pmol/L)	9.19-18.61	13.51 ±2.36	9.96-15.28	12.13 ±2.97	9.16-18.64	13.23 ±2.35	0.394
FT3 (2.2-6.8pmol/L)	2.10-3.7	2.88 ±0.44	2.61-2.99	2.8 ±0.2	2.09-3.7	2.88 ±0.44	0.7551

Note: asterisk (*) denotes statistical difference among the means.

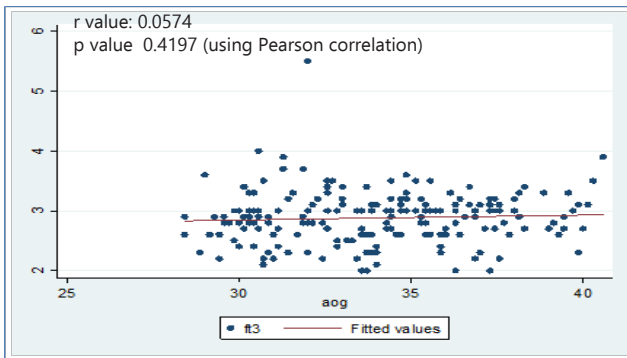


Figure 3: Free triiodothyronine scatter plot with fitted values

Relationship of Thyroid Function Tests with Pregnancy Trimesters

Patal et al. (2010) and Hamin et al. (2011) did previous studies on establishing the mean values and 2.5th to the 97.5th percentiles of TSH, FT3 and FT4 during the first and second trimesters in the pregnant Filipino who consulted at the PGH Obstetrics outpatient clinic.

Using ANOVA in comparing the three trimesters (Figure 4), it can be observed that the mean TSH was lowest during the first trimester but comparison across the trimesters was not significant (p value: 0.064).

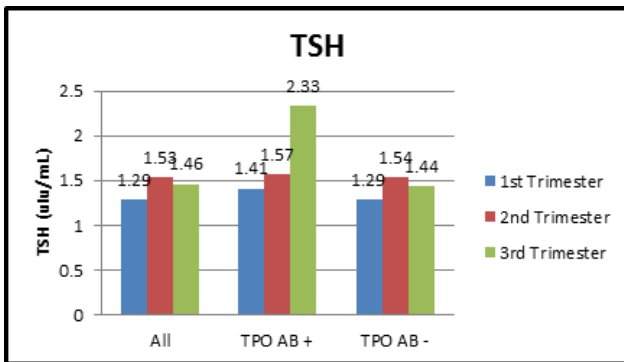


Figure 4: Mean thyrotropin in each pregnancy trimester

In the case of FT4 (Figure 5), means across the three trimesters shows significant difference (p value: 0.00). Using multiple pairwise comparison, it can be noted that the first trimester showed a significant higher mean compared with the second trimester (p value: 0.00) and with the third trimester (p value: 0.00), while there is no significant difference between the means of the second and the third trimesters (p value: 0.55).

In the case of FT3 (Figure 6), means across the three trimesters shows significant difference (p value: 0.00). Using multiple pair wise comparison, the third

trimester showed significantly lower mean compared with the first trimester (p value: 0.00) and with the second trimester (p value: 0.00) whereas there is no significant difference between the means of the first and the second trimesters (p value: 0.252).

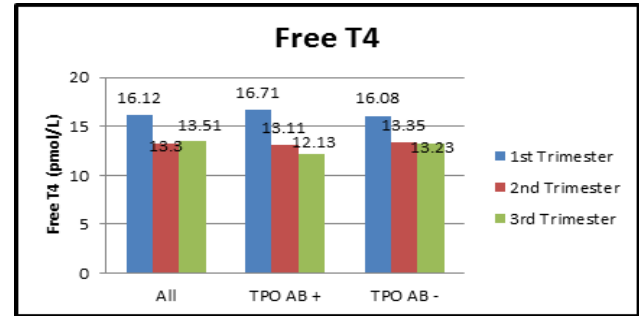


Figure 5: Mean free thyroxine in each pregnancy trimester

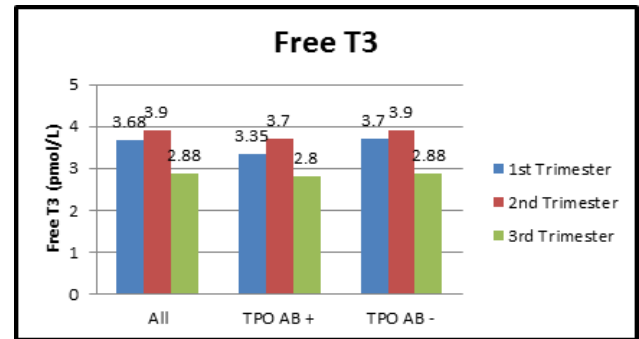


Figure 6: Mean free triiodothyronine in each pregnancy trimester

Discussion

The mean values of FT4 and FT3 between TPOAb-positive and TPOAb-negative subjects were not statistically significant while that of the TSH showed statistical significance, which may be due to the difference in the sample sizes of the two groups. This is also an expected finding of less than 10% TPOAb positivity in the general population of women in reproductive age group.

The increasing TSH trend as AOG increases is consistent with the results of both the first and second trimester thyroid function tests done by Patal et al. (2010) and Hamin et al. (2011), respectively. This TSH trend is similar to the studies done in China,¹³ Malaysia¹⁴ and Switzerland.¹⁸ The FT4 showed a decreasing trend as AOG increases which is consistent with the study done in China¹³ and India¹⁷ but is in contrast with the results of the first and second trimesters. Lastly, there is a non-significant decreasing trend of FT3 as AOG increases which is consistent with the first and second trimesters and has similar

Comparing the results of the thyroid function tests

done in the first, second and third trimesters, results in studies done in India¹⁷ and Spain.¹⁵

the first trimester showed the lowest actual mean TSH with significantly higher FT4 levels while the third trimester showed a significantly reduced FT3 level.

Conclusion

We have established the third trimester-specific reference intervals for thyroid function tests in TPOAb-negative pregnant Filipino patients with ranges as follows: TSH= 0.2-3.0 uIU/mL (N.V. 0.3-3.8 uIU/mL) ; FT4 = 9.16-18.64 pmol/L (11-24 pmol/L) and FT3= 2.09-3.7 pmol/L (N.V. 2.2-6.8 pmol/L).

Among the 200 pregnant Filipino women recruited, 197 (98.5%) were TPOAb-negative while 3 (1.5%) had positive titers. The TSH differed significantly between the two groups and is expected with the general population while the free T4 and T3 did not differ significantly.

In the TPOAb-negative patients, the levels of TSH and FT4 increase as pregnancy duration increases in the third trimester while FT3 showed no significant correlation with age of gestation.

Reference intervals change with pregnancy and throughout the course of pregnancy. Trimester-specific thyroid function tests established by the studies of Patal, et al., Hamin, et al. and this study was not able to replicate any of the reference intervals of the different countries with established trimester-specific thyroid hormone values, thus establishing the need for the Philippines' own reference intervals and will further aid in the management of the Filipinos.

Acknowledgement

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