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Reference Interval of Thyroid Stimulating Hormone and free Tetra-iodothyronine in Healthy Pregnant Women of Quetta, Baluchistan

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ABSTRACT

Objective: To establish the reference intervals of thyroid stimulating hormone and free Tetraiodothyronine in healthy pregnant women of Quetta, Baluchistan.

Study Design: Cross-sectional study.

Study Setting and Duration: Combined Military Hospital, Quetta Pakistan, at Jun 2018 to Jun 2019.

Methodology: Consecutive blood samples of healthy pregnant women (in all three trimesters) were taken to analyse thyroid stimulating hormone and free Tetra-iodothyronine by electrochemiluminescence immunoassay. For all three trimesters, the 5th and 95th percentiles were taken as reference intervals of thyroid stimulating hormone and free Tetraiodothyronine.

Results: A total of 388 blood samples were taken. Of these, 136 samples were from the first trimester. The mean age of the study population was 25.1±3.7 years in the first trimester, 26.7±4.5 years in the second trimester, and in the third trimester, it was 26.8±4.8 years. The reference interval for thyroid stimulating hormone in the first trimester was 0.6-3.3 uIU//ml, while it was 0.6-3.8uIU/ml and 0.6- 2.7uIU//ml during the second and third trimesters, respectively. Similarly, in the first-trimester reference interval for free Tetraiodothyronine was 9.8-18.0pmol/l. The values of free Tetraiodothyronine in the second and third trimesters were 10.4-20.1pmol/l and 11.0-20.9pmol/l, respectively.

Conclusion: All laboratories should establish reference intervals for thyroid stimulating hormone (TSH) to avoid misdiagnosing thyroid disorders during pregnancy.

Keywords: Reference interval, Pregnancy, Trimester, Thyroid stimulating hormone

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INTRODUCTION

Thyroid hormones are vital in fetal development, and their optimal function is also essential for the mother.[1] Therefore, the thyroid gland should be adequately functioning during pregnancy.[2] The foetus depends on the maternal thyroid hormone supply until its thyroid gland becomes functional, usually after the first trimester of pregnancy.[3,4]

Pregnancy causes numerous physiological changes in a mother. All these changes ensure that a sufficient amount of fuel and nutrients are supplied to the fetus.[5] These changes cause an increase in thyroid hormone secretion as the thyroid gland is stimulated by a surge of human chorionic gonadotropin (HCG), structurally, which resembles TSH. There is also an increased thyroid-binding globulin and altered iodide metabolism during pregnancy.[6] Maternal thyroid hormone production is also increased due to thyroid hormone degradation by placental type 3 Iodothyronine deiodinase.[7] Due to these changes, it is difficult to interpret thyroid function status in pregnant subjects. The hypermetabolic state during pregnancy further complicates the interpretation difficult due to the overlap of signs and symptoms with thyroid disorders. During pregnancy, thyroid hormone measurement can help monitor preexisting thyroid disease and rule out any suspected thyroid abnormality.[8,9]

Reference intervals for thyroid function are usually derived from non-pregnant subjects, which cannot be applied to interpret thyroid function in pregnant females. These non-pregnant cut-off values can be misleading during pregnancy. Therefore, populationbased reference intervals are essential to avoid misdiagnosing thyroid disorders during preg-nancy.[10] Our study aimed to establish a reference interval of thyroidstimulating hormone and free Tetraiodothyronine in all three pregnancy trimesters in the Quetta, Baluchistan population.

METHODOLOGY

This cross-sectional study was carried out at the Chemical Pathology Department, Combined Military Hospital, Quetta Pakistan , from June 2018 to June 2019. Non-probability consecutive sampling technique was used. A sample size of 338 was calculated using the WHO calculator, keeping the significance level at

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5% with a confidence level of 95% (prevalence of thyroid disease being 6%).[11] After approval from the Ethical Review Committee (ERC/IRB Approval No: CMH Qta/033) data were collected.

Inclusion Criteria: Healthy pregnant women having singleton pregnancy and without any known co-morbid, i.e. diabetes, hypertension, chronic liver disease, chronic kidney disease, pulmonary disease, or thyroid disorder were included on the study.

Exclusion Criteria: Pregnant women with a history of thyroid illness, hyperemesis gravidarum, antithyroid drugs use, those who developed other illnesses during pregnancy, and those with bad obstetric history were excluded from the study.

The gestational age was confirmed by the history of the Last Menstrual Period (LMP) and antenatal ultrasound scan. After taking informed consent, about 3.0ml blood sample was taken from each subject in a gel vacutainer. Serum TSH and FT4 were analyzed by electrochemiluminescence competitive binding assay technique on Cobas e401-Random Access Immunoassay System.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were summarized as mean±SD and qualitative variables were summarized as frequency and percentages. Reference intervals were taken as 5th and 95th percentiles for TSH and free T4 in all three trimesters of pregnancy.

RESULTS

Out of 388 pregnant women, 136(35.05%) were in the first trimester, 128(32.98%) were in the second, and 124(31.97%) women were in the third trimester of pregnancy (Table-I). The mean, percentiles and reference intervals for TSH and FT4 levels in all three trimesters were shown in the Table-II. The lower reference value of TSH was 0.6uIU/ml in all three trimesters. The upper reference value increased from 3.3uIU/ml to 3.8uIU/ml from the first to the second trimester but decreased to 2.7uIU/ml in the third trimester.

Table-I: Comparison of Study Population Characteristics and Thyroid Hormones (n=388)

Parameters	First Trimester	Second Trimester	Third Trimester
Age (years)	25.1±3.7	26.7±4.5	26.8±4.8
Number of subjects (%)	136(35.05%)	128 (32.98%)	124(31.97%)
Thyroid Stimulating Hormone (uIU/ml)	0.6-3.3	0.6-3.8	0.6-2.7
Free Tetraiodothyroni (pmol/l)	9.8-18.0	10.4-20.1	11.0-20.9

Table-III: Comparison of our Reference Intervals with American Thyroid Association (ATA) Guidelines 12 and Gilani et al.[17]

Trimesters	Our Reference Interval	Gilani *et al*Error! Bookmark not defined.17 Reference Interval	American Thyroid Association Guidelines12
	TSH uIU/ml		
1st Trimester	0.6-3.3	0.05-2.8	0.1-2.5
2nd Trimester	0.6-3.8	0.16-3.3	0.2-3.0
3rd	0.6-2.7	Not done	0.3-3.0

DISCUSSION

During pregnancy, the foetus depends on the mother's thyroid hormones, especially during its first weeks of life.[11] The mother thyroid gland adapts accordingly to meet the requirements of pregnancy by increasing its output of thyroid hormones. These hormones, by negative feedback, suppress the TSH.[12]

Due to these pregnancy-associated changes in thyroid hormones, it is difficult to interpret thyroid profiles using non-pregnant reference intervals. ATA has proposed cut-off values of thyroid hormones for pregnant women. However, geographic location and ethnicity have a significant impact on thyroid hormone levels which is reported by many studies.[13-15] For an appropriate diagnosis of thyroid status, all important parameters should be assessed, i.e. TSH, T4, T3, and antibodies affecting the thyroid gland, like anti-thyroid antibodies, and antithyroglobulin antibodies, should be investigated. TSH levels can give direction to the thyroid status, which may also serve as the primary screening marker for thyroid gland

Table-II: Thyroid Stimulating Hormone and FT4 Levels observed in the Study Population (n=388)

Trimesters	Parameters	Mean± SD	Confidence Interval	5th Percentile	50th Percentile	95th Percentile	Reference Interval
First	TSH (uIU/ml)	1.98±0.88	1.8-2.1	0.6	2.0	3.3	0.6-3.3
	T4(pmol/l)	13.7±2.6	1.8-2.1	9.8	13.6	18.0	9.8-18.0
Second	TSH (uIU/ml)	1.8±0.9	1.7-2.0	0.6	1.7	3.8	0.6-3.8
	T4(pmol/l)	14.8±2.8	1.7-2.0	10.4	14.5	20.1	10.4-20.1
Third	TSH (uIU/ml)	1.6±0.6	1.5-1.7	0.6	1.6	2.7	0.6-2.7
	T4(pmol/l)	15.6±2.9	1.5-1.7	11.0	15.7	20.9	11.0-20.9

TSH= Thyroid-Stimulating Hormone FT4= free Tetraiodothyronine SD= Standard deviation

disorder.[16]

Our reference intervals were also significantly different from non-pregnant reference intervals (0.4-4.5uIU/ml) and those proposed by the American Thyroid Association (Table-III).

Due to the presence of thyroid-binding protein in abnormal concentrations in different physiological states that can affect hormone binding, FT4 was done instead of total T4 (TT4), which is a better parameter in assessing the thyroid status. ATA recommends the use of assay, population & trimester-specific reference intervals in pregnant women.[4,12]

Hyper-functioning of the thyroid gland during pregnancy was reported in our study population, which has been documented by other authors as well.[1,3,7,17,18] In our study, the lower reference value of TSH for three trimesters was 0.6mIU/l which, compared to ATA guidelines, is higher for all three trimesters. Furthermore, the upper reference limit for TSH for all trimesters was higher than ATA cut-off values. TSH values increased from the first to the second trimester, which is also agreed by similar studies. Gilani *et al.* in 2018 reported the same results and TSH values increased as the pregnancy progressed, but their reference intervals were much lower than our reference intervals.[17] These differences may be because of different geographic locations and the iodine status of the population. Khalil *et al.* documented that the upper reference value of TSH for the first trimester was 3.33uIU/ml, the same as reported in our study population (3.3uIU/ml).[10] Another study reported that the upper reference value for the second trimester in the Asian population was 3.64uIU/ml, which was again close to our value for the second trimester (3.8uIU/ml).[13]

Solidin *et al.* from the USA, also reported a lower upper value of TSH in the third trimester, which is also consistent with our study.[19] Marwaha *et al*. from India, Yan *et al.* from China and Azizi *et al.* from Iran also reported similar results.[18,20,21] In their study, Marwaha *et al.* also mentioned a lower upper reference limit of TSH in the third trimester compared to the first and second trimesters, as in our study. However, their reference range was much higher than ours.[18] The free T4 increased throughout the pregnancy, which is also reported by many other studies. Further-more, we noted that mean TSH values decreased as the pregnancy advanced. The value during the first trimester was higher than the other two trimesters. Such findings are inconsistent with other studies, meaning TSH increased as pregnancy progressed.[8,17]

LIMITATIONS OF STUDY

Our study has certain limitations. Due to limited resources, we could not assess other important markers like T3, TPO, and antithyroglobulin antibodies. Moreover, it was a single-centred study, and we could not confirm iodine status by urinary iodine measurement test.

CONCLUSION

Under and overdiagnosis of thyroid status can be avoided by using trimester-specific cutoff values for thyroid hormones in pregnancy. The results of our study would be helpful for better diagnosis and management while treating pregnant women of Baluchistan with thyroid malfunction.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AK & NA: Conception, drafting the manuscript, approval of the final version to be published.

R & TAK: Study design, data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AK & SSM: Drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Xing J, Yuan E, Li J, Zhang Y, Meng X, Zhang X, et al. Trimester- and Assay-Specific Thyroid Reference Intervals for Pregnant Women in China. Int J Endocrinol 2016; 2016: 3754213. doi: 10.1155/2016/3754213.
2. Stricker R, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA, et al. Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. Eur J Endocrinol 2007; 157(4): 509-514. doi: 10.1530/EJE-07-0249.
3. Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? Clin Chem 2015; 61(5): 704-713. doi: 10.1373/clinchem.2014.236646.
4. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21(10): 1081-125. doi: 10.1089/thy.2011.0087.
5. Ramachandran R, Mohan L, Jose MS. Prevalence of thyroid disorders in antenatal women and its impact on maternal and foetal outcome. Indian J Forensic Community Med 2020; 7(1): 29-32. doi:10.18231/j.ijfcm.2020.008.
6. Moon HW, Chung HJ, Park CM, Hur M, Yun YM. Establishment of trimester-specific reference intervals for thyroid hormones in

Korean pregnant women. Ann Lab Med 2015; 35(2): 198-204. doi: 10.3343/alm.2015.35.2.198.
7. Mankar J, Sahasrabuddhe A, Pitale S. Trimester specific ranges for thyroid hormones in normal pregnancy. Thyroid Res Pract 2016; 13(3): 106-109. doi: 10.4103/0973-0354.180192.
8. Jebasingh FK, Salam R, Meetei TL, Singh PT, Singh NN, Prasad L. Reference intervals in evaluation of maternal thyroid function of Manipuri women. Indian J Endocrinol Metab 2016; 20(2): 167-170. doi: 10.4103/2230-8210.176354..
9. Thevarajah M, Chew YY, Lim SC, Sabir N, Sickan J. Determination of trimester specific reference intervals for thyroid hormones during pregnancy in Malaysian women. Malays J Pathol 2009; 31(1): 23-27.
10. Khalil AB, Salih BT, Chinengo O, Bardies MRD, Turner A, Abdel Wareth LO. Trimester specific reference ranges for serum TSH and Free T4 among United Arab Emirates pregnant women. Pract Lab Med 2018; 12(1): e00098. doi: 10.1016/j.plab.2018.e 98.
11. Khan A, Khan MA, Akhtar S. Thyroid Disorders, Etiology and Prevalence. J Med Sci 2002; 2(2): 89-94. doi: 10.3923/s.2002.89. 94
12. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27(3): 315-389. doi: 10.1089/thy.2016.0457. Erratum in: Thyroid 2017; 27(9): 1212.
13. La'ulu SL, Roberts WL. Second-trimester reference intervals for thyroid tests: the role of ethnicity. Clin Chem 2007; 53(9): 1658-1664. doi: 10.1373/clinchem.2007.089680.
14. Rajput R, Singh B, Goel V, Verma A, Seth S, Nanda S. Trimester-specific reference interval for thyroid hormones during pregnancy at a Tertiary Care Hospital in Haryana, India. Indian J Endocrinol Metab 2016; 20(6): 810-815. doi: 10.410545643/2230-8210.192545454903.
15. McNeil AR, Stanford PE. Reporting Thyroid Function Tests in Pregnancy. Clin Biochem Rev 2015; 36(4): 109-126.
16. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012; 18(6): 988-1028. doi: 10.4158/EP12280.GL. Erratum in: Endocr Pract 2013; 19(1): 175.
17. Gilani M, Asif N, Akram A, Gilani M, Ijaz A, Malik SS. Determination of reference intervals of thyroid markers during pregnancy in Urban area of District Rawalpindi Pakistan. J Pak Med Assoc 2018; 68(10): 1488-1492.
18. Marwaha RK, Chopra S, Gopalakrishnan S, Sharma B, Kanwar RS, Sastry A, et al. Establishment of reference range for thyroid hormones in normal pregnant Indian women. BJOG 2008; 115(5): 602-606. doi: 10.1111/j.1471-0528.2008.01673.x.
19. Soldin OP, Soldin D, Sastoque M. Gestation-specific thyroxine and thyroid stimulating hormone levels in the United States and worldwide. Ther Drug Monit 2007; 29(5): 553-559.
20. Yan YQ, Dong ZL, Dong L, Wang FR, Yang XM, Jin XY, et al. Trimester- and method-specific reference intervals for thyroid tests in pregnant Chinese women: methodology, euthyroid definition and iodine status can influence the setting of reference intervals. Clin Endocrinol (Oxf) 2011; 74(2): 262-269.
21. Azizi F, Mehran L, Amouzegar A, Delshad H, Tohidi M, Askari S, et al. Establishment of the trimester-specific reference range for free thyroxine index. Thyroid 2013; 23(3): 354-359. doi: 10.10 89/thy.2012.0407. Erratum in: Thyroid. 2013 ; 23(7): 915.

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