ORIGINAL ARTICLE

Can serum ferritin predict thyroid performance in the first trimester?

Roaa Mokram Hamed,[1] Wassan Nori,[2] Zina Abdullah Hussein[3]

Abstract

Objectives: The primary aim of the study was to establish a reference value for the thyroid hormone in the first trimester of pregnancy in Iraq's population. The second aim was to look into the correlation between iron deficiency anaemia and thyroid hormone.

Methods: In a cross-sectional study conducted at the National Center of Haematology, 74 consented pregnant women at a gestational age < 13 weeks were recruited. An estimation was made for iron indices [haemoglobin, serum ferritin] and Thyroid Function Test [Triiodothyronine, Thyroxine and Thyroid-stimulating hormone] via collected blood samples.

Result: The reference value for thyroid hormones was 1.79±2.05 pmol / l for Thyroid-stimulating hormone, 4.59±3.35 pmol / l for Thyroxine and 191±62.1 ng/dl for Triiodothyronine. Correlation showed an inverse relationship of Thyroid-stimulating hormone with serum haemoglobin and a positive correlation between Triiodothyronine and Thyroxine versus serum haemoglobin and ferritin. Mallow's coefficient of correlation evaluated the strength of the association between serum haemoglobin against Thyroid-stimulating hormone, Triiodothyronine, and Thyroxine. The strongest association was for Thyroxine.

Thyroid-stimulating hormone, Thyroxine, and Triiodothyronine taken as independent variables were challenged against serum ferritin and haemoglobin as dependent variables. The only significant correlation was for serum ferritin and thyroid markers.

Conclusion: First-trimester screening for ferritin, in addition to routine haemoglobin testing, can reveal masked depleted iron stores. Hidden thyroid disease can be associated with anaemia, so Thyroid-stimulating hormone screening is recommended. Early diagnosis of these deficiencies in the first trimester will stop their impact on both the foetus and the mother's well being.

Keywords: Iron deficiency anemia, Thyroid hormone, Ferritin, First trimester. (JPMA 71: S-3 [Suppl. 9]; 2021)

Introduction

The source of life is said to be blood. Haemoglobin, a glycoprotein iron-containing molecule, is the responsible factor. Haemoglobin concentrations below 13 mg/ml in adults and 11 mg/ml in pregnant women are considered as anaemia (A).[1,2] One-quarter of the world's population suffers from A, rendering it a global health problem. Iron deficiency anaemia (IDA) has a frequency of 20% in pregnancy due to rising demands and depleting stores, particularly if there is not enough spacing between them, as seen in our Iraqi population. Many medical and therapeutic studies focused on A because of the wide variety of implications for both mother and foetus.[3] The production of thyroid hormone is increased as pregnancy progresses. It is essential for the growth and neurodevelopment of the new foetus. Nervous tissue starts to develop during the second month of pregnancy. This vital hormone deficiency can lead to irreversible damage, stunting children's milestones, and impends normal mental development. Consequently, a child will suffer from lower intelligence quotients and poor school performance. Moreover, a subclinical goitre can lead to recurrent abortion and sub-fertility and prematurity.[4,5]

Thyroid diseases are common in pregnancy and the postpartum period as subclinical hypo-thyroiditis is blamed for postpartum Blues.[6] Pregnancy influences the reference values of thyroid function tests (TFTs). Overlooking gestation-specific reference intervals will misidentify maternal thyroid disease;[7] Springer D et al. discussed that many misdiagnoses occur in the first trimester, particularly with Thyroid-stimulating hormone values.[8] The level of stored iron in our bodies is determined by a blood protein called ferritin, irrespective of recent iron intake. Serum ferritin < 30 g/L is considered a gold standard for IDA diagnosis 1. Both A and hypothyroidism have a negative impact on foeto-maternal wellbeing.[9] This study verifies the correlation between maternal thyroid hormones and serum ferritin among the pregnant Iraqi population in the first trimester.

Patients and Methods

A case-control descriptive study was conducted in the national centre of haematological diseases, which deals with hundreds of anaemia cases every month. The study was conducted from April 2019 to 2020, in Baghdad, Iraq.

[1]The National Center of Hematology, [2,3]Department of Obstetrics and Gynaecology, Mustansiriyah University, Baghdad, Iraq.

Correspondence: Wassan Nori. Email: dr.wassan76@uomustansiriyah.edu.iq

The ethics committee issued ethical approval for the research (MOG 89 on 23rd-April-2019). All volunteers gave informed consent before participation. Seventy-four pregnant women who met the inclusion criteria were recruited. The inclusion criteria were; gestational age < completed 13 weeks of singleton pregnancy estimated based on an early ultrasound scanning or menstrual cycle days. Only primigravida and multiparous females delivered within the last two years who had not started vitamin supplements, were included.

Based on a detailed history, a thorough general examination with a neck exam for any signs of goiter was done. Pregnant women with a history of hypothyroidism, diabetes mellitus, chronic and pregnancy-induced hypertension, a history of renal disease, and smoking were excluded. Participants with a history of abruptio placentae, multiple unexplained pregnancy loss and preterm labour were also excluded. Venous blood was obtained in EDTA vials after a one-night fast for haemoglobin evaluation using the full blood count system on an electronic haematology analyser DxH520 (Beckman Coulter Sn BC010420, Germany) depending on WHO guidelines. In pregnant women, A was described as a haemoglobin level < than 11 g/dl. Approximately 5 mL of venous blood was stored aseptically in a simple vacutainer to measure ferritin and thyroid function test [Triiodothyronine, Thyroxine, and Thyroid-stimulating hormone]. Serum was isolated and processed at -20°C (TSH, T4andT3). The ferritin level was determined using an ELISA immunoassay. The thyroid function test was analysed by an Immunoassay system (Beckman Colter, Inc.A99558A. Germany). The local trimester-specific reference values following the recommendation Guidelines of the Endocrine Society was implemented as reference values.

Continuous data were expressed as a range, Mean ± Standard deviation were analysed by Student t-test. Categorical variables were expressed by percentage and frequencies and compared with Chi-Square Test. The association between study parameters Triiodothyronine, Thyroxine, Thyroid-stimulating hormone, haemoglobin, ferritin versus Triiodothyronine, Thyroxine as an independent marker, and haemoglobin as a dependent marker were calculated by a series of linear regression equations. To measure the magnitude of the correlations between study markers, the best subset regression model and Mallow's coefficient of correlation was applied which specified the strongest factor. Partial line square fit PLS estimated correlations between haemoglobin and serum ferritin against Triiodothyronine, Thyroxine, and Thyroid-stimulating hormone. P-value was significant at <0.05 for all.

Results

This study examined 74 pregnant females at a gestational age < 13 weeks. Regarding their demographic criteria, age range was 16-36 years, parity ranged from 1-4. Lab. test results are expressed as mean ±SD as follows:

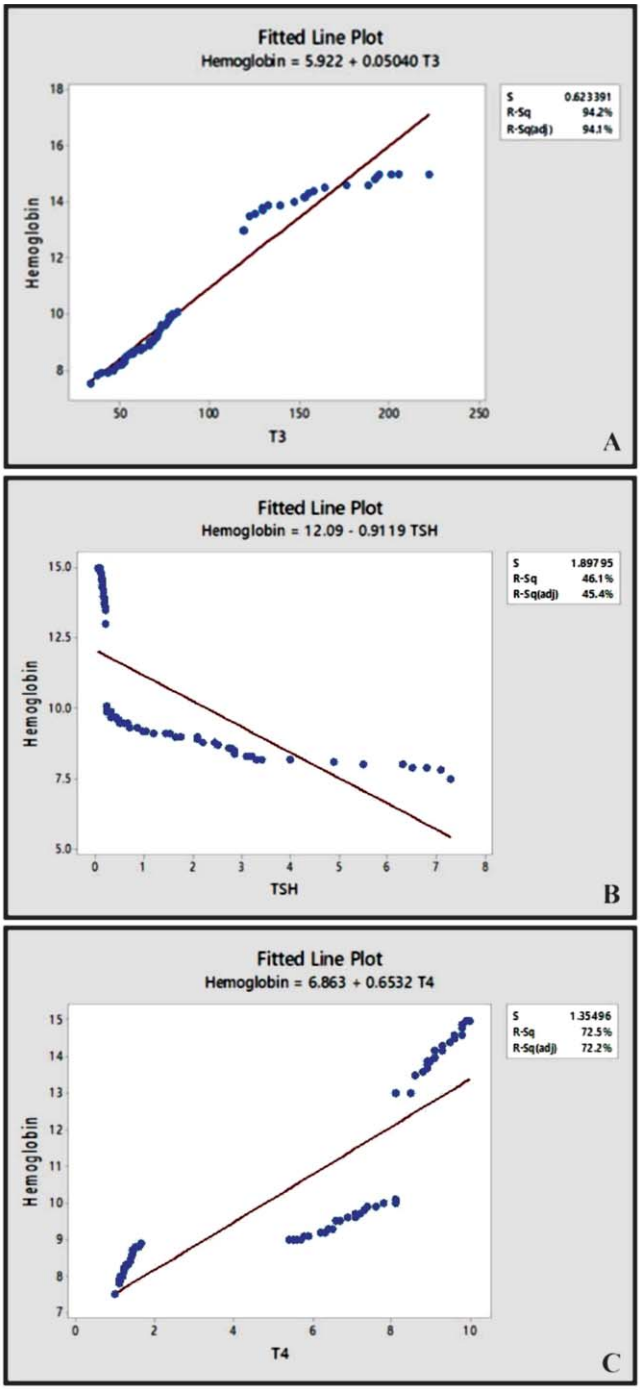

Figure-1: Thyroid-stimulating hormone shows a negative correlation with serum haemoglobin (fig.1 B). Triiodothyronine and Thyroxine showed a positive correlation to serum haemoglobin, as seen in fig. 1A and fig.1C, respectively.

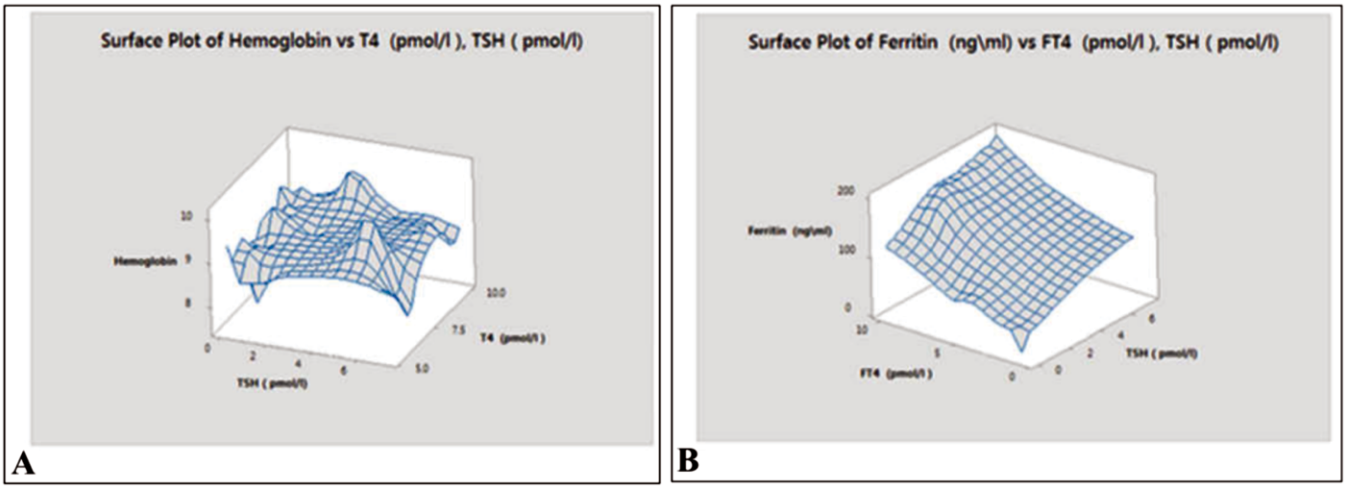

Figure-2: A) Surface plot showing no correlation between haemoglobin versus Thyroxine and Thyroid-stimulating hormone. Figure-2: B) Surface plot highlighting a strong direct correlation between serum ferritin versus Thyroxine and Thyroid-stimulating hormone.

Table: Showing the best Subsets Regression for thyroid hormones, the coefficient of mallows is interpreted as the highest correlation for the smallest generated value, shown for Thyroxine hormone.

The variance	R-Sq	Coefficient of mallows (Cp)
Thyroid-stimulating hormone	94.3	13.91
Thyroxine	95	2.2**
Triiodothyronine	95.2	4.1

**Most significant Mallows coefficient of correlation was between hemoglobin versus Thyroxine.

Haemoglobin (11.6±2.57) gr/dl, serum ferritin (46.17±22.04) ng/ml, Thyroid-stimulating hormone (1.79±2.05) pmol/l, Triiodothyronine (191±62.1) ng/dl, and Thyroxine (4.59±3.35) pmol/l.

Pearsons correlation showed a negative relationship of TSH with serum Hb and a positive correlation between Triiodothyronine and Thyroxine versus serum haemoglobin and ferritin; all were highlighted in 3-dimensional Figure-1. The mallows coefficient (cp) measured the association between serum haemoglobin aginst Thyroid-stimulating hormone, Triiodothyronine, and Triiodothyronine. Cp is interpreted as the strongest association for the lowest value, seen between Thyroxine with haemoglobin demonstrated in Table.

Finally, Triiodothyronine, Thyroxine, and Thyroid-stimulating hormone taken as independent variables were challenged against serum ferritin and haemoglobin as dependent variables. The result was significant for serum ferritin and thyroid markers, as illustrated in Figure-2.

Discussion

The analysis showed a direct relationship between serum Thyroid-stimulating hormone versus ferritin levels and a negative correlation between serum Thyroid-stimulating hormone and serum ferritin values. This gestational age was chosen because the iron needs are minimal and to overcome haemodilution effects.[2] In addition, patient selection was limited to those who had given birth in the previous two years since thyroid anomalies seen during pregnancy can lead to postpartum thyroiditis so that they can be an extension to a previous pregnancy.[10] Thyroid hormone reference levels in the first trimester of Iraqi women are as follows: (1.79±2.05) pmol/l, (4.59±3.35) pmol/l, and (191±62.1) ng/dl for Thyroid-stimulating hormone, Thyroxine, and Triiodothyronine, respectively.

Thyroid-stimulating hormone, Thyroxine, and Triiodothyronine were measured in Iran by Kianpour M et al.[11] and found the following results: (1.84± 1.33), (1.01± 0.16), and (4.50± 0.63) pmol/l, respectively. As for China, J Fu et al. found median values of (1.53), (10.43), and (4.50) pmol/L in China.[12] The discrepancy may be caused by differences in iodine consumption, racial and anthropomorphic differences within each country.

To measure thyroid disease in pregnant women, the Endocrine Society (ES) and the American Thyroid Association (ATA) recommend using a population-based trimester-specific reference set. They aimed for the reduction of needless medications, tests, hormone assessments. When these ranges are unavailable, the ATA recommends using a Thyroid-stimulating hormone of 4mIU/L within the first trimester. Many healthy pregnant women will be misclassified as pathological if standardisation screening is not used.[13,14]

Gu Y et al.[15] found an important positive association between free thyroid hormone concentrations and A and greater anaemia rates in overt hypothyroidism and euthyroid cases. In line with previous research, our

findings revealed an inverse association between Thyroid-stimulating hormone and serum haemoglobin.[16,17]

Iodine and iron are two important microelements needed by the gland. Iron is essential in a variety of metabolic and enzymatic reactions. Thyroid peroxidase (TPO), a haem-dependent enzyme in the thyroid gland, is one of them. When an iron deficiency occurs, thyroid peroxidase function is decreased.[4,18]

The association between serum haemoglobin and ferritin levels against Thyroid-stimulating hormone, Triiodothyronine, and Thyroxine demonstrated that serum ferritin, not serum haemoglobin, was closely linked to thyroid hormone. Ferritin is a measure of overall body iron stores. It is the first variable to shift as iron stores fall, regardless of recent iron consumption. Its level changes in hypothyroidism due to a decline in total iron storage indicators.[19]

Shuxiang Li et al.[20] measured A and hypothyroidism correlation; he estimated the impact of autoantibodies on the magnitude of A, a criterion not considered by this study. Flora Veltri et al. focused on thyroid hormone impact on A and autoantibody titer at a lower serum ferritin cutoff value of 15g/L compared to the 25 cutoff value used by this study. Flora Veltri et al. study declared a specificity of 98 per cent and a sensitivity of 75 percent.[21] Iron deficiency anaemia could be the haematological manifestation of hypothyroidism and even the first symptom that leads to a diagnosis. Any case of A resistance to iron therapy should be considered as a differential diagnosis for hypothyroidism.[22]

This study sets a standard reference value for pregnancy-specific Thyroid-stimulating hormone reference values in Iraqi women. Since hypothyroidism shows no clinical symptoms, it is diagnosed on Thyroid-stimulating hormone reference levels;[14] this is a crucial point; applying a precise reference will identify hidden cases and reduce the wide range of complications from abortion, abruptio placenta, preterm labour, growth restriction, respiratory distress syndrome and pre-eclampsia.[23-25]

The study has its limitations; we excluded iodine, an essential mineral for thyroid function.

Iodine tends to reduce the gland's iron-stimulating effect. Another worth mentioning point is that autoimmune antibodies were not considered, which are a frequent cause of hypothyroidism during pregnancy and plays a key role in developing anaemia in women of childbearing age.

Conclusion

The results of this study established local reference ranges for pregnant Iraqi females. The population-based, trimester-specific reference range must be adjusted. Thyroid gland disease alters the metabolism of serum iron. Treatment of IDA counteracts thyroid dysfunction. We recommend screening for Thyroid-stimulating hormone and serum ferritin as they can coexist together.

Acknowledgement: We are grateful to the University, Al Mustansiriyah, for continuous support.

Disclaimer: None.

Conflict of Interest: None.

Funding Disclosure: None.

References

1. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet 2016;387:907-16. doi: 10.1016/S0140-6736(15)60865-0.
2. Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188:819-30. doi: 10.1111/bjh.16221.
3. Abdul-Fatah BN, Murshid RM, Ahmed TE. Assessment of Iron Deficiency Anemia (IDA) and Dietary Pattern among pregnant women in Baghdad City, Iraq. J Pharm Sci Res 2018;10:2279-84.
4. Korevaar TIM, Tiemeier H, Peeters RP. Clinical associations of maternal thyroid function with foetal brain development: Epidemiological interpretation and overview of available evidence. Clin Endocrinol (Oxf) 2018;89:129-38. doi: 10.1111/cen.13724.
5. Nori W, Abdulghani M, Roomi AB, Akram W. To operate or to wait? Doppler indices as predictors for medical termination for first trimester missed abortion. Clin Exp Obstet Gynecol 2021;48:168-74. DOI: 10.31083/j.ceog.2021.01.2215
6. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015;3:286-95. doi: 10.1016/S2213-8587(14)70225-6.
7. Zhang D, Cai K, Wang G, Xu S, Mao X, Zheng A, et al. Trimester-specific reference ranges for thyroid hormones in pregnant women. Medicine (Baltimore) 2019;98:e14245. doi: 10.1097/MD.0000000000014245.
8. Springer D, Jiskra J, Limanova Z, Zima T, Potlukova E. Thyroid in pregnancy: From physiology to screening. Crit Rev Clin Lab Sci 2017;54:102-16. doi: 10.1080/10408363.2016.1269309.
9. Rosario PW, Carvalho M, Calsolari MR. TSH reference values in the first trimester of gestation and correlation between maternal TSH and obstetric and neonatal outcomes: a prospective Brazilian study. Arch Endocrinol Metab 2016;60:314-8. doi: 10.1590/2359-3997000000132.
10. Wade AN, Mandel SJ. Thyroid disease and pregnancy. In: Cooper DS, Sipos JA, eds. Medical Management of Thyroid Disease, 3rd ed. Boca Raton, Florida: CRC Press, 2019; pp 275-97.
11. Kianpour M, Aminorroaya A, Amini M, Feizi A, Janghorbani M. Thyroid function test reference ranges in the first trimester of gestation and pregnancy outcomes: Protocol and preliminary results for cohort population-based study Isfahan, Iran. J Res Med Sci 2018;23:e99. doi: 10.4103/jrms.JRMS_197_18.
12. Fu J, Yang A, Zhao J, Zhu Y, Gu Y, Xu Y, et al. The relationship between iron level and thyroid function during the first trimester of pregnancy: A cross-sectional study in Wuxi, China. J Trace Elem

Med Biol 2017;43:148-52. doi: 10.1016/j.jtemb.2017.01.004.
13. 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;27:315-89. doi: 10.1089/thy.2016.0457.
14. Castillo Lara M, Vilar Sánchez Á, Cañavate Solano C, Soto Pazos E, Iglesias Álvarez M, González Macías C, et al. Hypothyroidism screening during first trimester of pregnancy. BMC Pregnancy Childbirth 2017;17:438. doi: 10.1186/s12884-017-1624-x.
15. Gu Y, Chi VTQ, Zhang Q, Liu L, Meng G, Wu H, et al. Low-Normal Thyroid Function Predicts Incident Anemia in the General Population With Euthyroid Status. J Clin Endocrinol Metab 2019;104:5693-702. doi: 10.1210/jc.2019-00888.
16. Correia Nóbrega AG. Micronutrient Influence in Thyroid Function: A Review. Int J Nutrol 2019;12:52–60. DOI: 10.1055/s-0039-3402028.
17. Xu L, Port M, Landi S, Gemignani F, Cipollini M, Elisei R, et al. Obesity and the risk of papillary thyroid cancer: a pooled analysis of three case-control studies. Thyroid 2014;24:966-74. doi: 10.1089/thy.2013.0566.
18. Szczepanek-Parulska E, Hernik A, Ruchała M. Anemia in thyroid diseases. Pol Arch Intern Med 2017;127:352-60. doi: 10.20452/pamw.3985.
19. Li S, Gao X, Wei Y, Zhu G, Yang C. The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy. J Nutr Sci Vitaminol (Tokyo) 2016;62:397-401. doi: 10.3177/jnsv.62.397.
20. Veltri F, Decaillet S, Kleynen P, Grabczan L, Belhomme J, Rozenberg S, et al. Prevalence of thyroid autoimmunity and dysfunction in women with iron deficiency during early pregnancy: is it altered? Eur J Endocrinol 2016;175:191-9. doi: 10.1530/EJE-16-0288.
21. Soppi E. Iron deficiency is the main cause of symptom persistence in patients treated for hypothyroidism. Thyroid 2015;25(Suppl 1):A74.
22. Nori W, Ali AI. Maternal alpha-1-antitrypsin as a noval marker for growth restriction in pre-eclampsia. J Obstet Gynaecol Res 2021;47:4250-5. doi: 10.1111/jog.15043.
23. Lee SY, Cabral HJ, Aschengrau A, Pearce EN. Associations Between Maternal Thyroid Function in Pregnancy and Obstetric and Perinatal Outcomes. J Clin Endocrinol Metab 2020;105:e2015–23. doi: 10.1210/clinem/dgz275.
24. Nori W, Roomi AB, Akram W. Platelet indices as predictors of fetal growth restriction in Pre-eclamptic Women. Rev Latinoam Hipertens 2020;15:280-5. DOI: 10.5281/zenodo.4442971