ORIGINAL ARTICLE

EXPLORING THE RELATIONSHIP BETWEEN THYROID STIMULATING HORMONE (TSH) AND FERRITIN IN THE THIRD TRIMESTER: IMPLICATIONS FOR FETAL OUTCOMES

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ABSTRACT

Objective: Thyroid diseases affect 2%-33% of pregnant women. Maintaining TSH levels during pregnancy is crucial for normal thyroid function, and iron deficiency undermines thyroid hormone synthesis and metabolism. Understanding these relationships can optimize maternal and neonatal health. This research aims to explore this connection.

Materials & Methods: This cross-sectional study was conducted at Darul-Sehat Hospital, involving 174 participants with a 13.2% prevalence of thyroid dysfunction in the third trimester of pregnancy. Convenience sampling was used, enrolling women with singleton pregnancies in labor regardless of iron supplementation status. Demographic and medical details were recorded. Blood specimens were collected for CBC, TSH, and Ferritin during the third trimester or at the onset of labor. Neonatal outcomes included birth weight, Apgar score, birth defects, low birth weight, preterm birth, birth asphyxia, hyperbilirubinemia, hypothyroidism, and NICU admissions.

Results: In this study, 20.6% of neonates were preterm, and 47.7% were admitted to NICU. TSH and Apgar scores were significant, with p-values of 0.05 and 0.03. A significant weak inverse correlation was seen between TSH and serum ferritin levels (P-value<0.05).

Conclusion: The research findings indicate a notable negative association between maternal TSH and serum ferritin concentrations, demonstrating a connection where decreased iron reserves are associated with elevated TSH levels

Keywords: Pregnancy, Thyroid Stimulating Hormone, Serum Ferritin, Third Trimester, Neonate

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INTRODUCTION

Pregnancy embodies a significant phase of physiological adjustment distinguished by complex hormonal and metabolic alterations. Within this context, the maternal thyroid function and iron metabolism are pivotal in facilitating fetal growth and development. [1] Thyroid hormone is vital for fetal neurodevelopment, while adequate iron stores are essential for erythropoiesis and oxygen transport. [2] Despite their significance, emerging evidence suggests a potential interplay between thyroids function and iron metabolism during pregnancy. [3]

In women of reproductive age, thyroid diseases are the second leading cause of endocrine disorders affecting at least 2%–3% of pregnant women. [4] Pregnancy-related hypothyroidism is more common in low and middle-income nations than in developed nations, with reports ranging from 5 to 31.6%. [5] According to recommendations of the European Endocrine Society, TSH levels should be maintained between 0.2-<2.5 mU/L in the first trimester of pregnancy and between 0.3-3 mU/L in the 2nd and 3rd trimesters. [6] A variety of trace elements are necessary for normal thyroid function, and iron is one of them. Iron deficiency undermines the synthesis and metabolism of thyroid hormones. [7]

Given the intertwined roles of thyroid hormones and iron in fetal development, understanding their relationship may provide valuable insights into optimizing maternal and neonatal health outcomes. Prior research has suggested a possible connection between thyroid

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dysfunction and iron deficiency in pregnant women. To our knowledge, not much work is done on Pakistani women. Nonetheless, the exact dynamics of this association and its influence on the health of the fetus are not fully grasped. The primary objective of this research is to address this knowledge gap by thoroughly examining the correlation among maternal TSH levels, serum ferritin levels in the third trimester of pregnancy, and fetal outcome

MATERIALS AND METHODS

After receiving approval from the institutional review board (DSH/IRB/2022/0014), this cross-sectional study was carried out in the Obstetrics and Gynecology and Pediatric department at Darul Sehat Hospital from March 2022 to October 2022. To achieve a 95% confidence level with a ±5% margin of error, a sample size of 174 participants was determined based on a 13.2% prevalence of thyroid dysfunction in the third trimester of pregnancy, utilizing the WHO sample size calculator. [8] A non-probability convenience sampling approach was utilized, enrolling women with singleton pregnancies in their third trimester who were in labor, regardless of their iron supplementation status during pregnancy. Exclusion criteria encompassed women with multiple pregnancies or underlying conditions such as diabetes mellitus, hypertension, renal disorders, or other medical ailments.

Following the acquisition of verbal informed consent, interested individuals were enrolled in the study. Comprehensive demographic and medical details of the participants were recorded, and a thorough general physical examination in addition to a pelvic ultrasound was performed to determine gestational age and ensure normal pregnancy progression. Blood specimens were collected from all participants during the third trimester, and for those who were unbooked, samples were obtained at the onset of labor to analyze complete blood count (CBC), thyroid-stimulating hormone (TSH), and serum ferritin levels. The gathered data was duly documented, and upon delivery, information regarding the mode of delivery and neonatal outcomes was meticulously noted. Neonatal assessments involved parameters such as birth weight, Apgar score, presence of birth defects, occurrence of intrauterine growth restriction (IUGR), low birth weight, preterm birth, birth asphyxia, hyperbilirubinemia, hypothyroidism, as well as Neonatal Intensive Care Unit (NICU) admissions, accompanied by the reasons for admission.

Data analysis will be done using SPSS version 23. For quantitative variables such as demographic features and lab investigations mean and standard deviation is recorded. Qualitative variables are reported as frequency and percentages. To test for association, a chi-square test will be applied keeping a p-value of <0.05 as statistically significant. Normality of the data was checked by the Shapiro-Wilk test. Due to the non-normal distribution of all continuous variables, they were presented as Median (interquartile range) while categorical variables were presented with frequency (percentages). Mann Whitney U test and chi-squared test were applied to compare variables between groups. Spearman correlation was used to check the relationship between variables. A correlation coefficient of <0.3 was considered a weak correlation, a correlation coefficient between 0.3 to 0.7 was considered a moderate correlation, and a correlation coefficient of >0.7 was considered a strong correlation. P-value<0.05 was statistically significant.

RESULTS

Overall, 174 pregnant women participated in the study with a median (IQR) age of 30 (25-33) years. The median (IQR) of the gravida, parity, and non-viable pregnancies were 2 (1-4), 1 (0-2) and 0 (0-1) respectively. The Median (IQR) of Hemoglobin, Hematocrit, MCV, MCH, MCHC, and TLC in 3rd trimester were observed to be 10.45(9.9-11.3), 32(31-34), 82.5(79-87), 28(26-30), 32(31-33), and 8400(7400-9850) respectively. Eight-eight (50.6%) women had serum ferritin levels between 15-30 mcg/L. Peripheral film at booking visit demonstrated that normocytic normochromic was present in the majority of women (66.7%), followed by microcytic hypochromic in 24.1%, normochromic anisocytosis in 4.6 %, normocytic hypochromic in 2.9 %, and macrocytic presented in only 1.7% women. Most of the women (78.7%) were taking oral iron supplements whereas the rest were taking injectable iron supplements (21.3%). The frequency of hypothyroidism was found to be 12.1%. Table 1 presented a comparison of baseline characteristics between women with euthyroid and hypothyroid. No significant difference was observed in any parameter.

Most of the women had elective LSCS 71 (40.8%), followed by normal vaginal delivery 60 (34.5%) and emergency LSCS 38(21.8%). Only 03 had VBAC (1.7%) while 02 had instrumental vaginal delivery (1.1%).

Data presented as n (%) or median (interquartile range); P-value<0.05 is considered to be statistically significant.

In this study 36(20.6%) neonates were born Preterm, with low birth weight being 28(16%). 83 (47.7%) neonates were admitted to NICU. Moderate to severe hyperbilirubinemia was seen in 37(21.2%) neonates requiring Phototherapy. The analysis revealed no significant difference in mode of delivery, gestational age, NICU admission, and various neonatal parameters including birth weight and bilirubin level (P-value$>$ 0.05). Notably, TSH and Apgar scores were significant with p values of 0.05 and 0.03 respectively as shown in Table 2 Data presented as n (%); P-value<0.05 considered to be statistically significant

DISCUSSION

Thyroid dysfunction during pregnancy has been increasingly recognized for its potential to adversely affect both maternal and fetal health. [9] Iron deficiency impairs thyroid function by disrupting thyroid peroxidase activity, essential for hormone synthesis, leading to elevated TSH levels and potential hypothyroidism during pregnancy. [10, 11]

The results of our study discovered a weak but significant inverse link between maternal TSH and serum ferritin levels in the third trimester, implying that lower iron stores are linked to higher TSH levels. Maternal hypothyroidism was associated with elevated neonatal TSH levels, while no significant associations were found with other fetal outcomes.

Iron deficiency may impair thyroid function during pregnancy, emphasizing the necessity for integrated monitoring and treatment of both conditions. The weak inverse correlation between maternal TSH and serum ferritin levels suggests that pregnant women with higher TSH levels may have lower iron stores, potentially impacting iron metabolism. Monitoring and managing both thyroid function and iron levels is crucial for optimal maternal and fetal health outcomes.

A study conducted in China in 2022 showed an association in pregnant women between their iron status and thyroid hormone levels, SF and Hb were negatively correlated with TSH, and a similar result was found in our study. [12] Similar results were found in a study conducted in India by Gupta et al. but it was conducted in the first trimester so the fetal outcome was not assessed.

The results suggest that lower ferritin levels are linked to higher TSH levels, indicating a potential relationship between iron deficiency and thyroid function in pregnant females during the first trimester. [13] A study conducted in Bulgaria during the third trimester of pregnancy showed a strong positive correlation between TSH (thyroid-stimulating hormone) and serum ferritin levels. This correlation indicates a parallel increase of TSH secretion induced by decreased thyroxine concentration, reflecting the dynamic interplay between iron and thyroid status in pregnant women, as compared to this our study discovered a weak but significant inverse link between maternal TSH and serum ferritin levels in the third trimester implying that lower iron stores are linked to higher TSH levels. [14]

A study conducted in Hyderabad showed the frequency of thyroid disorders in anemic pregnant women to be 23.5% during 1st trimester of pregnancy, highlighting the fact that screening for thyroid disorders in iron-deficient anemic women should be considered to offer well-timed treatment for avoiding the related complications. However this study only iron-deficient women were screened. [15]

Iron deficiency was not found to be significantly associated with hypothyroidism in the study conducted at JSS Hospital in India, contrary to expectations based on previous research and the results of our study linking iron and thyroid status in pregnant women. [16]

Our findings are consistent with other studies which showed an inverse relationship of maternal ferritin with the weight of newborns at birth. [17 and 18] Maternal iron accumulation has been proposed to raise blood viscosity, which could lead to poor uteroplacental circulation and, ultimately, poor fetal development. [19]

Our study has revealed a weak insignificant correlation between maternal ferritin and neonatal hyperbilirubinemia. A nested case-control study by Mohamad Ali Moghimi et al. compared excess iron supplementation

Table No 1: Baseline characteristics of participants concerning thyroid categories

Parameters	Euthyroid	Hypothyroid	P-value	Overall
N	153(87.9%)	21(12.1%)		174
Maternal age (years)	30(25-33)	30(25-33.5)	0.937	30(25-33)
Gravida	2(1-4)	2(1-4)	0.705	2(1-4)
Parity	1(0-2)	1(0-3)	0.501	1(0-2)
Non-viable pregnancies	0(0-0)	0(0-1)	0.620	0(0-1)
Hemoglobin	10.5(10-11.3)	10.4(9.5-11.3)	0.666	10.45(9.9-11.3)
Hematocrit	32(31-34)	32(28-33)	0.129	32(31-34)
Serum ferritin	15(9.35-22.5)	12(8.8-22.5)	0.592	15(9.38-22.25)
Serum ferritin < 15 mcg/L	75(49%)	11(52.4%)	0.773	86(49.4%)
Serum ferritin 15-30 mcg/L	78(51%)	10(47.6%)		88(50.6%)
Iron supplementation				
Oral iron	123(80.4%)	14(66.7%)	0.149	137(78.7%)
Injectable iron	30(19.6%)	7(33.3%)		37(21.3%)

Table No 2: Association with mother's ferritin levels with neonatal outcome

		weight of baby at birth				P value	Total
		<1.5	**1.6-2.4**	2.5-3.5	>3.5		
	serum ferritin < 15 mcg/L	1(33.3)	9(36)	70(51)	6(66.6)		86
	serum ferritin >15-30mcg	2(66.6)	16(64)	67(48.9)	3(33.3)	0.34	88
Total		3(1.7)	25(14.4)	137(78.7)	9(5.2)		174
		total bilirubin				**P value**	**Total**
		<9.9	10-15.9	16-19.9	>20		
	serum ferritin < 15 mcg/L	37(56)	35(49.2)	12(36.3)	2(50)		86
	serum ferritin >15-30mcg	29(43.9)	36(50.7)	21(63.6)	2(50)		88
Total		66(37.9)	71(40.8)	33(19)	4(2.3)		174
		gestational age at delivery				P value	Total
		32-36	37-42				
	serum ferritin < 15 mcg/L	17(47.2)	69(50)			0.76	86
	serum ferritin >15-30mcg	19(52.7)	69(50)				88
Total		36(20.7)	138(79.3)				174
		TSH of baby				P value	Total
		<8	>8				
	serum ferritin < 15 mcg/L	82(48.2)	4(100)				86
	serum ferritin >15-30mcg	88(51.7)	0			*0.05	88
Total		170(97.7)	4(2.3)				174
		NICU admission				P value	Total
		yes	no				
	serum ferritin < 15 mcg/L	35(42.1)	51(56)				86
	serum ferritin >15-30mcg	48(57.8)	40(43.9)			0.67	88
Total		83(47.7)	91(52.3)				174
		Apgar score at 1 minute				P value	Total
		4-6	>7				
serum ferritin	serum ferritin < 15 mcg/L	5(26.3)	81(52.2)			*0.03	86
	serum ferritin >15-30mcg	14(73.6)	74(47.7)				88
Total		19(10.9)	155(89.1)				174

Data presented as n (%); P-value<0.05 considered to be statistically significant

Table No 3: Association of maternal ferritin with neonatal outcomes

Parameters	r	P-value
Weight of baby at birth	-0.135	0.037
Apgar score at 1 minute	-0.162	0.016
TSH of baby	-0.155	0.020
Total bilirubin	0.124	0.051
Gestational age at delivery	-0.023	0.384
NICU admission	-0.139	0.034

r: correlation coefficient; P-value<0.05 considered to be statistically significant

may be associated with neonatal hyperbilirubinemia. [20]

This study is subject to various limitations. To begin with, its observational methodology does not permit the establishment of a causal relationship between thyroid function and iron levels. Moreover, the relatively small sample size of 174 female participants may lack representativeness of the broader population, thus affecting the generalizability of the results.

This research emphasizes the importance of monitoring thyroid function and iron levels in pregnant women to optimize maternal and fetal health. An analysis shows a correlation between maternal TSH and serum ferritin levels, indicating a thyroid-iron interplay. Maternal hypothyroidism may influence neonatal TSH levels, but further research is needed on other fetal outcomes. More investigation is warranted to understand the interconnected mechanisms and support updated clinical guidelines. The findings are consistent with the hypothesis, showing a strong link between elevated maternal TSH levels and decreased serum ferritin levels, backing the anticipated connection between thyroid activity and iron processing. Moreover, the documented relationship between maternal hypothyroidism and increased neonatal TSH levels validates the assumption about its impact on fetal thyroid operation.

CONCLUSION

The research findings indicate a notable negative association between maternal TSH and serum ferritin concentrations, demonstrating a connection where decreased iron reserves are associated with elevated TSH levels. This implies that insufficient iron levels could hinder thyroid functionality in pregnant individuals. Analysis of neonatal results revealed no substantial distinctions, apart from elevated TSH levels in the offspring of mothers with hypothyroidism. These results emphasize the importance of comprehensive monitoring of both iron and thyroid levels in pregnancy to enhance the well-being of both the mother and the fetus.

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Authors Contribution:

Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Munaver SA	✓	×	✓	×	✓	×
Bham SQ	✓	✓	×	✓	✓	×
Shaheen N	×	✓	×	×	✓	×
Akhter AN	✓	✓	✓	×	✓	✓

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.

Ethical Approval:

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