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Correlation between Thyroid Hormones Levels and Some Sex Hormones in Pregnancy States

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ABSTRACT

Thyroid diseases in pregnant women pose a significant challenge for physicians, affecting 1.2% of pregnancies. Untreated conditions can lead to obstetric complications and fetal development disorders, including placental abruption, preeclampsia, preterm birth, and fetal death. This research aims to compare levels of thyroid hormones with female sexual hormones such as estrogen and progesterone due to the change in their levels and to establish the relationship between BMI and (T3 and T4) every third during pregnancy. The research included measuring thyroid hormones that include the hormones triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH). These hormones are associated with female sexual hormones, including progesterone and estrogen, during the three trimesters (first, second, and third). The findings showed that TSH (thyroid-stimulating hormone) levels in the second and third trimesters of pregnancy were significantly different from those in the control group, while the results showed that arose significantly for both hormonal T3 and T4 at all three stages of pregnancy as compared to control at a significant level ($p \leq 0.05$). According to the results, body mass index (BMI) increased significantly during pregnancy, with the third trimester experiencing the greatest increase compared to the control group. The third trimester of pregnancy experienced the biggest increase in female sex hormones compared to the control group, with levels of estrogen and progesterone peaking during these three trimesters ($p \leq 0.05$). During the three pregnancy periods, progesterone and estrogen demonstrated a significant and opposite connection with thyroid-stimulating hormone (TSH) compared to the control group ($p \leq 0.05$). The research aims to investigate the impact of pregnancy trimesters on thyroid and sexual hormones and the need for improved diagnosis and treatment, especially in the first three months of each phase.

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INTRODUCTION

Gestational is a physiological condition that causes important changes in the thyroid's function, and many factors contribute to this change from the start of gestation. Due to a similar composition of the hormone human chorionic gonadotropin (HCG) emitted via the membranes of the placenta as well as the thyroid stimulating hormone (TSH), which stimulates the thyroid gland. This increases gland secretion for the hormone TSH and lowers levels of both T3 and T4 during the first three months of gestation (Kostecha-Matyja et al., 2017). It has been observed that these hormonal changes in pregnant women include a rise in iodine requirements pregnant women experience hormonal changes such as increased iodine requirements due to thyroid hormone generation, enhanced kidney secretion, increased thyroid hormone concentration, decreased blood albumin, and stimulation of thyroid hormone receptors by human placental genitalia (Khalil et al., 2018).

These alterations are to blame for thyroid function tests noted during gestation (Li et al., 2014). There is a change in thyroid function and secretion during pregnancy compared to pre-pregnancy (Kumar et al., 2017). Also, weight

change is common in females with thyroid disorders, and it has been shown (Solanki et al., 2013) that TSH levels in the blood are positively associated with body mass index (BMI) during pregnancy (Nyrnes et al., 2006), BMI increases significantly due to normal weight gain as pregnancy progresses, the exact relationship between gland function and BMI is not clearly defined in pregnant women, research has indicated that between 45 and 65 percent of the entire variation in thyroid function is brought about by genetic agents, the remainder was influenced by several factors including ecological agents such as iodine condition as well other properties such as BMI (Medici et al., 2017).

The thyroid gland is made up of several spherical compositions called vesicles, which secrete amino hormones, containing iodine, represented by thyroxine (T4) as well triiodothyronine (T3), Called thyroid hormones. The thyroid is also composed of pleural follicle cells, which lie between the follicles and secrete a peptide hormone called calcitonin. This hormone does not contain iodine and is one of the hormone para thyroids (Vanderpump, 2011).

Alterations in thyroid function during gestation lead to increased metabolic conditions and hormonal stimulus of the thyroid axis. The triiodothyronine T3 and thyroxine T4 ratios are increasing by 30–100 due to the thyroid gland response to high globulin levels associated with the gland and the increased fetal need for thyroid hormones during the initial months of gestation (Dai et al., 2020, Wu et al., 2021).

Female sex hormones play an important role during pregnancy. Pregnancy is influenced by the hormone estrogen, and if it decreases, it originates from many sources such as ovulatory bulbs as well as fatty tissues. Despite the circumstances that influence the production of estrogen, there aren't normal cases in which gestation and natural delivery occur in the total absence of estrogen, and high levels of this hormone stimulate increased hepatic manufacturing by thyroxine-binding globulin (TBG), whereby increased secretion of TSH, which in turn enhances thyroid hormone production (Skjoldebrand et al., 1986). As well as progesterone, which has a major effect during gestation, includes preventing the mom's immune tract from rejecting the embryo and assisting in preventing contractures and inflammation till delivery, Cathey and colleagues demonstrated that progesterone levels in the expectant mother are rising, indicating the activity of the yellow body to ensure the fetus' survival and also play a significant role in promoting the formation of blood vessels into the endometrium (Cathey et al., 2019). The importance of the research study is to compare levels of thyroid hormones with female sexual hormones such as estrogen and progesterone due to the change in their levels and to establish the relationship between BMI and (T3 and T4) every third during pregnancy.

MATERIALS AND METHODS

The study involved 70 women between the ages of 15 and 45 and was separated into two groups. The first included 45 pregnant women who were divided into three stages, each stage including 15 women per third of pregnancy, respectively, and a control group of 25 non-pregnant females was identified, as well as a body mass index (BMI) of kg/m² for both groups. Samples of blood were taken from a vein of 5 ml from each patient and put in test tubes free of any preservatives to separate the blood to obtain the serum using a centrifuge at 3000 cycles per minute for five minutes (Tietz, 1994).

Then the serum was pulled using a micropipette and put in a plastic test tube for biochemical tests on it. The concentration of thyroid hormones, which include Tri-iodothyronine (T3), thyroxine hormone (T4), thyroid-stimulating hormone (TSH), and female sex hormones such as progesterone, were analyzed using a special measurement kit called the Fluorescence Immuno Assay (FIA) equipped with the Korean AFIAS-6 for the quantitative determination of hormones in human serum/plasma. The analysis uses a sandwich immunodetection method, where detector antibodies bind to sample antigens, forming complexes, and migrate onto a nitrocellulose matrix for capture by immobilized-streptavidin on test strips, resulting in a stronger fluorescence signal (Wilson et al., 1981; Oneil & Editor, 2001).

Estrogen hormone was analyzed using a special measurement ELISA kit equipped by Nandino Blvd/USA. The principle of the assay is ELISA (enzyme-linked immunosorbent assay) for the quantitative analysis of estrogen in biological fluid. This test kit uses a microplate coated with an antibody to detect the enzyme conjugate and estrogen in a sample. The enzyme conjugate is added to the sample, and the plate is incubated for one hour. The enzyme conjugate is detected by adding substrate, and quantitative results are

obtained by measuring absorbance readings against standards (Sadem et al.,1979).

The length and mass of patients and the control group have been measured, as well as (BMI), according to the following equation (Walker & Edwards, 1999).

$$\text{Body mass index (BMI)} = \frac{\text{weighing (in kilos)}}{\text{Tallness (meter)}^2}$$

Statistical analysis

The data were analyzed by finding the mean rate and standard deviation using an ANOVA; the correlation factor test between the chemo-biomarkers and the thyroid stimulating hormone was used in the three gestational periods; the test of the coefficient of association between BMI and female hormones with thyroid hormones (T3, T4) was adopted during the first three months of pregnancy using a test person; and the statistical analysis was considered statistical evidence at a level of ($p \leq 0.05$) (Williams, 2017).

RESULTS AND DISCUSSION

The study found no significant difference in BMI in the first three trimesters of pregnancy, but two-thirds of second and third pregnancies showed a significant rise ($p \leq 0.05$) compared to the control group. There was a significant correlation between BMI and TSH, as illustrated in Table 2, possibly due to increased leptin hormone secretion by fatty tissue in obese individuals, which affects hypothyroidism functions by organizing thyroid-releasing hormone (TRH) (Mosso et al., 2016; Kumar et al., 2017).

Table 1. Relationship between the levels of female sex hormones T3, T4, and TSH, throughout three pregnancies (first, second, and third trimesters)

Mean ± SD
Age (15-45) year
Pregnancy periods

Biochemical parameters	Controls n=25	1st trimester (1-12 wk) n=15	2nd trimester (13-27 wk) n=15	3rd trimester (28-40 wk) n=15
BMI Kg/m²	22.21±1.92 (a)	22.40±1.80 (a)	27.62±2.65 (b)	33.00±3.92 (c)
FT3 nmol/mL	1.87±0.16 (a)	2.47±0.05 (b)	3.61±0.16 (d)	2.95±0.48 (c)
FT4 nmol/mL	76.40±6.33 (a)	104.95±3.52 (b)	120.55±6.74 (c)	127.85±4.126 (d)
TSH Miu/mL	1.49±0.68 (b)	1.62±0.13 (bc)	0.47±0.13 (a)	1.90±0.17 (c)
Progesterone Nmol/L	5.99±2.44 (a)	90.48±38.19 (a)	218.35±173.25 (b)	474.36±239.77 (c)
Estrogen Pg/mL	69.24±21.20 (a)	104.76±641.42 (b)	339.36±234.90 (c)	438.98±126.37 (d)

BMI=body mass index

FT3=free triiodothyronine

FT4=free thyroxine

TSH=thyroid stimulating hormone

1ST Trimester=first trimester

2nd Trimester =second trimester

3rd Trimester =third trimester

SD=standard deviation

Table 2. Calculating the correlation coefficient between thyroid-stimulating TSH hormone levels and female sex hormones per third during pregnancy

	Biochemical parameters				
Groups	**T3 and TSH (r)**	**T4 and TSH (r)**	**BMI and TSH (r)**	**Progesterone and TSH (r)**	**Estrogen and TSH (r)**
control	0.001*	0.181*	0.81	-0.107*	0.166*
1st Trimester (1-12) wk	-0.177	0.030	0.389*	0.472	0.132
2nd Trimester (13-27) wk	-0.585*	0.010	0.293	0.399*	0.034
3rd Trimester (28-40) wk	-0.291*	-0.272*	0.559*	0.566*	-0.176*

r= correlation coefficient

*Statistically significant ($p \leq 0.05$)

Table 3. Testing correlation coefficient among body mass index and the pregnancy hormones T3, and T4 during the three gestational phases

	Biochemical parameter	
groups	**BMI and T4 (r)**	**BMI and T3 (r)**
Control	0.652**	-0.051
1st Trimester (1-12) wk	-0.060	-0.204
2nd Trimester (13-27) wk	-0.038*	-0.172
3rd Trimester (28-40) wk	-0.293*	0.163*

r= Correlation coefficient

*Statistically significant ($p \leq 0.05$)

**Statistically significant ($p \leq 0.01$)

Table 4. Calculating the correlation coefficient between thyroid hormones T3, and T4 with female sexual hormones in three trimesters: first, second, as well third of gestation

	Hormones concentrations			
groups	**Pro.(r) T4**	**Pro.(r) T3**	**Est.(r) T4**	**Est.(r) T3**
Control	0.136	-0.224	-0.236	0.310
1st Trimester (1-12) wk	0.079	-0.334	-0.594*	0.194
2nd Trimester (13-27) wk	0.256	0.018	-0.038	-0.165*
3rd Trimester (28-40) wk	0.153	-0.458	-0.245	-0.244

Est = Estrogen

1st= First trimester

2nd= Second trimester

3rd= Third trimester

r= Correlation coefficient

*Statistically significant ($p \leq 0.05$)

Different characters show that there are statistically significant differences between groups at level ($p \leq 0.05$) according to the ANOVA test. Table 3 explains a negative and significant correlation between T4 and body mass index (BMI) in the second and third gestations, and elevated serum T4 levels are linked to decreased BMI in pregnant women. It was noted that the hormone T3 has a positive relationship with BMI, especially during the third stage of gestation. When compared with the control group, this goes back to the variation in thyroid functionality in expectant women, which is related to changes in body weight and BMI. The causes may be simple or multi-factor, but the biological mechanism is still not fully known. Therefore, BMI can be used to show abnormal thyroid functionality in expectant women (Gowachirapant et al., 2014).

Collares et al. (2017) and his group referred to the decline in T4 level during the initial stage of gestation as linked to a high BMI, but there is no significant connection between the two-thirds of the second and third gestations. This might be a result of a difference in every third pregnancy. Biologically, the level of the hormone T4 speeds up the metabolism. This is what explains the link between T4 and BMI during the initial stage of gestation (Sheng et al., 2018). According to Sentis et al., 2021, the main job of the hormone T3 is to raise energy use and heat production to maintain the body's weight gain in balance. This means that when people lose weight, their serum T3 levels drop. It could be because of the T3 adaptive mechanism that makes fat build-up (Silvestri et al., 2005). Leptin changes the level of T3 by increasing the effectiveness of the deiodinase enzyme, which then changes T4 to T3. These changes in levels of thyroid hormone in obese people are considered a result of overweight modifications (Sheng et al., 2018).

The results shown in Table 1 indicate a significant difference ($p \leq 0.05$) for hormones T3, and T4 at all three stages of pregnancy in comparison with the control group. In the third stage of pregnancy, there was a significant rise in the hormone T4. There was also an increase in T3 levels in the second trimester of pregnancy compared to the control group ($p \leq 0.05$), which suggests that the rise in these hormones is due to higher levels of the hormone human chorionic gonadotropin. Since the initial three months of pregnancy, it has been directly stimulating the thyroid-stimulating hormone TSH, so that the structural similarity of HCG and TSH leads to increasing serum levels of both T3 and T4 and prevents TSH secretion. TSH is located in the blood at (0.1 Miu/mL), which is merely a tiny portion (five percent) in women by the eleventh week of pregnancy (Korevaar et al., 2017).

Thyroid-stimulating hormone (TSH) levels are elevated as a result through the third stage of gestation, and the upper limit of T4 in the first and second trimesters is also high. There are reduced levels of T4 in the third stage of pregnancy, which is different from the results of his study (Zhang et al., 2019), and these results can be relied upon to diagnose thyroid disorders, which have relied mainly on the changing values of T4 and TSH.

As shown in Table 2, there is a strong negative relationship between TSH and T3 levels during the second and third gestations of pregnancy compared to a control group ($p \leq 0.05$). This might be due to Graves' disease, an autoimmune condition that produces antibodies against the recipient, or it might be due to an enlarged thyroid gland (hypothyroidism), which results from a direct decrease in the average amount of inorganic iodine ingested. The thyroid hormone is responsible for activating many proteins and thus stimulating response systems, any imbalance in this immune response disrupts thyroid hormone release (Devereaux & Tewelde, 2014; Lefevre, 2015).

The reverse significant correlation was also observed amongst TSH, and T4 in the third stage of gestation as explained in (Table 2), due to that levels of TSH it was negatively linked to T4 in the first stage of gestation research has shown the presence of this negative association because of the relapsing characteristics of human chorionic gonadotropin, yet the first ten weeks of gestation, hormone levels of these glands decrease later, leading to the lower level of T4 and increase the levels of TSH, in addition, high estrogen levels lead to high levels of globulin associated with thyroid hormone and thus increase levels of T4 and that's what a study has confirmed (Alexander, 2014; Kiran et al., 2021) about the coefficient of negative correlation between T4, TSH (Kharb et al., 2014).

As observed in Table 1, there are significant variations among the second and third pregnancies. During the different periods for the thyroid-stimulating hormone TSH, compared to a control group at a level ($p \leq 0.05$), the hormone's value increased in the initial trimester of pregnancy, decreased in the second, and then gradually rose in the final stage of pregnancy. That is due to the

editing of the Gonadotropin-releasing hormone (GnRH) on the eighth day of pregnancy, from the placental feeding cell and then begins to decline in the tenth week and then decreases after the twelfth week until the end of pregnancy, it then gradually begins to rise, this rise, in turn, showed a role similar to that of TSH, particularly in the first stage of gestation, it operates as a catalyst factor for the thyroid gland and has an impaired activity of about one-tenth of the strength of the TSH by activating the TSH, so the activity of the chorionic gonadotropins reach their peak by the late first stage of pregnancy, and maximum between the ninth and eleventh week. of pregnancy, then it decreases in the second stage until it increases gradually in the third trimester of pregnancy, and that's agreed with the study he came up with (Moon et al., 2015; Kostecha-Matyja et al., 2017).

A significantly lower TSH value was observed during the second trimester of gestation at a level of ($p \leq 0.05$) in comparison to the control group. So, it is hard to determine the minimum concentration of TSH because of its strong interaction with HCG, which substantially lowers the level of TSH during this period. This, in turn, is not similar to the diagnosis of hyperthyroidism (Khalid et al., 2014), and that's the same as what he said (Idris et al., 2005; Van-Trotsenburg, 2020); that weakness in thyroid function in pregnancy, where the secretion is about 94% of thyroid hormones, like six percent of T3 as well as thyroxine (T4). Early detection of hypothyroidism during gestation is necessary for the prevention of unfavorable effects on the mother and embryo.

The reason for the differences in the TSH value during the three gestation periods, as contrasted with many studies, is perhaps because embryos can manufacture thyroid hormone after 16–18 weeks independently, but they still need thyroid hormone supplements for the mother, which are still crucial for fetal development, especially in two-thirds of the first and second pregnancies (Moon et al., 2015; Yim, 2016). According to Table 1, there is a significant, gradual rise in the hormone level during pregnancy compared to a control group ($p \leq 0.05$), it amounted to its highest level in the third stage of gestation. In turn, through an association of progesterone levels with the three pregnancy periods, this concentration increased in the third trimester in comparison to the first trimester of gestation. During the first ten weeks of pregnancy, the corpus luteum cyst in the ovary helps to change the uterine epithelium. This makes it possible for the blastocyst to interact with the uterine epithelium in a way that protects the fetus's survival. It produces blast cells with increased levels of the hormone stimulating human chorionic gonadotropin (HCG), this, in turn, stimulates the continuation of progesterone production and also has an important role in enhancing the blood vessels in the uterine lining (Schock et al., 2016).

There was a significant reverse link between progesterone and TSH during two-thirds of the second and third pregnancies in comparison to the control group ($p \leq 0.05$) in Table 2. This led to a contrast between thyroid function and the increased danger of gestation. As a thyroid hormone stimulates an increase in human chorionic gonadotropin (HCG), estrogen, progesterone, and human placental lactogen (HPL) hormone release through the placenta during gestation, it is crucial for sustaining a pregnancy (Maruo et al., 1991; Adu-Gyamfi et al., 2020).

Table 1 shows that there were significant differences ($p \leq 0.05$) in estrogen levels at all stages of pregnancy in comparison to the control group. The highest significant rise was seen in two-thirds of the second and third pregnancies, as shown in Table 2. There was also a significantly negative association between estrogen and TSH during the second and third trimesters compared to the control group. This result is consistent with what it says (Cotzias et al., 2008; Kostecha-Matyja et al., 2017). High levels of estrogen stimulate increased hepatic manufacturing by the globulin associated with the thyroid hormone thyroxine-binding globulin (TBG), which is one of the proteins associated with TSH. It increases the excretion of TSH, which motivates the thyroid gland to produce more estrogen during the advanced stages of pregnancy (Akarsu et al., 2016).

It also confirmed his study (Schock et al., 2016) about the rise in estrogen levels through the third stage of gestation, such an increase is giving rise to raising the activity in placental function during pregnancy. While the results are shown in Table 4, the absence of any significant sign of progesterone hormone indicates a relationship with T3 and T4. However, there is a strong reverse link between estrogen T3 and T4 in two-thirds of the first and second stages of pregnancies, this could be interpreted as a result of an imbalance in the estrogen hormone, which leads to dysfunction in the placenta and thus pregnancy disorder (Khadem et al., 2012; Conde-Agudelo and Romero, 2016).

The mechanism of change in the levels of T3 and T4 is unclear, as he pointed out (Skjoldebrand et

al., 1986; Kamel, 2022) in this study that the interactions between the hormones TSH, estrogen, and TBG can be explained by the decline of transit stimulus influence from HCG in the thyroid gland in early gestation. That may decrease thyroid hormone secretions and reduce its negative reaction on the pituitary axis (Lazarus, 2011; Awede et al., 2018; Mahadik et al., 2020). According to Smith et al., the reverse association between estrogen and T4 means that higher levels of estrogen have led to higher levels of globulin, which is linked to thyroid hormone. This has caused a rise in the T4 level.

CONCLUSION

Our study found that TSH, which rises in the third trimester, is the most essential hormone during gestation. BMI also showed a positive link with TSH and T3, as it showed a negative correlation with T4. Moreover, the third trimester of pregnancy saw increased female sex hormones, with estrogen and progesterone levels increasing throughout these trimesters.

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