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# Thyroid Function Tests and Thyroid Antibody Tests in Ectopic Pregnancies: A Prospective Cohort Study

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**ABSTRACT**

Thyroid hormone levels have been observed to induce structural changes in different regions of the fallopian tube. This study aimed to investigate the impact of thyroid hormones on ectopic pregnancy.

In pursuit of this objective, 31 patients with ectopic pregnancy were monitored at Siirt University Training and Research Hospital between July 2022 and December 2022. Additionally, a total of 31 patients with normal first-trimester pregnancies, matched for age, parity, and gestational week, were included in the control group. Various parameters, including patient age, pregnancy history, medical history, treatment methods, clinical and demographic data, TSH, fT3, fT4, TT3, TT4, Thyroglobulin, Anti-thyroglobulin Antibody, TSH receptor antibody (TrAB), Anti-Peroxidase Antibody, Anti-Tyroglobulin Antibody, hemogram, biochemistry, CRP, and sedimentation values, were compared.Clinical Trials no: NCT05446012

Statistically significant differences were noted in Free T3 (p = 0.011) and thyroglobulin (p = 0.018) values between the ectopic pregnancy and control groups. Subsequent ROC analysis was conducted for the significant parameters, determining the AUC (Lower and Upper Bound), sensitivity, specificity, and cut-off values for each parameter. Multivariate logistic regression analysis followed, wherein the "backward stepwise model" was applied to the Free T3 parameter. The apparent parameter indicating an increased risk in the disease was Free T3, with a 4.2-fold increase and a 95% CI of [1.3-13.5]. Lower Free T3 levels were associated with an elevated risk of ectopic pregnancy.

The assessment of Free T3 levels during pre-pregnancy counseling may aid in identifying pregnant women at risk of ectopic pregnancy.

**Keywords:** Ectopic, pregnancy, thyroid, hormones

## Introduction

Ectopic pregnancy is characterized by the implantation of the embryo outside the uterine cavity, predominantly occurring in more than 98% of cases within the fallopian tubes (1). Early detection of ectopic tubal pregnancies can often be effectively treated through minimally invasive surgery or medical management using methotrexate. However, in an unstable patient, particularly in the case of a ruptured ectopic pregnancy, immediate surgical intervention is crucial, accounting for 2.7% of pregnancy-related deaths (2,3).

The fallopian tubes play a crucial role in transporting gametes and embryos into the endometrial cavity, providing an optimal environment for fertilization and early embryonic development (4). While the etiology of ectopic pregnancy remains unclear, tubal implantation is likely due to impaired embryo-tubal transport, stemming from changes in the tubal environment (5). Risk factors, including a history of pelvic inflammatory disease, cigarette smoking, fallopian tube surgery, ectopic pregnancy, and infertility, likely impact the tubal environment and motility, influencing the transport of fertilized ovum into the uterine cavity.

Effective tubal transport of ova, sperm, and embryos is essential for a successful spontaneous pregnancy. Although much is yet to be uncovered about the mechanisms involved, it is evident that tubal passage is a more complex process than expected. The propulsion of gametes and embryos is achieved through a complex interaction involving muscle contractions, ciliary activity, and the flow of tubal secretions. Accumulating evidence emphasizes the importance and possibly the superior role of ciliary

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movement in this process. Various hormonal and neuronal factors modulate ciliary activity by altering the ciliary beat frequency in the fallopian tube (7). The characteristics of ciliated and secretory epithelial cells and smooth muscle layers vary throughout the oviductal regions, corresponding to the function of each region (8).

Recognizing the tube as an endocrine organ affected by endocrine changes (9), ongoing evidence supports the significant role of thyroid hormone in regulating reproductive tissues at various levels (10). However, the effects of thyroid disorders on tubal activity are not fully understood. Rat studies have indicated the presence of thyroid hormone receptors in the tubal epithelium and smooth muscle cells, designating the uterus and oviduct as active sites for thyroid hormones (11).

An experimental animal study highlighted the essential control of thyroid hormones over glycogen and lipid storage, lipid signaling, and lymphocyte infiltration in maintaining the microenvironment in rat fallopian tubes. Hypothyroidism increased the size of epithelial cells in various regions. This microenvironment is crucial for fertilization, sperm capacitation, and gamete development (12). In another experimental animal study, changes in the size of the fallopian tube epithelium and cell metabolism in hypothyroid rabbits were thought to affect oviductal activity and reproductive function (13).

Based on this information, our objective is to explore the potential relationship between Thyroid Function Tests and Thyroid Antibody Tests and ectopic pregnancies in humans.

## Materials and Methods

For this study, 40 patients diagnosed with ectopic pregnancy were monitored at Siirt University Training and Research Hospital from July 2022 to December 2022. The clinical trial commenced with the registration of the first patient on July 6, 2022. Nine patients who voluntarily left the hospital, had missing file information, or declined follow-up were excluded from the study. A total of 31 patients, matching the control group in terms of age, parity, BMI, and gestational age, were included. These patients had a normal first-trimester pregnancy and no history of thyroid disorders. The study received approval from the institutional Siirt University ethics board committee under the number "2022/01.03" and adhered to the Declaration of Helsinki standards. Clinical Trial Registration Number: NCT05446012.

Clinically suspected ectopic pregnancy was defined based on two criteria in the medical records. Confirmation of the diagnosis often involved serial evaluation through transvaginal ultrasonography and measurement of serum hCG levels. Transvaginal ultrasound findings showing specific signs, such as hematosalpinx or a lateral uterine gestational sac with an empty uterus, were considered. Patients with ectopic pregnancies in locations other than the fallopian tubes or of unknown location were excluded. Criteria for non-doubling βhCG levels after 48 hours, low decrease, and abnormalities in serial βhCG measurements were applied. To exclude early spontaneous abortions, only patients with an empty uterus and a sonographically suspected tubal ectopic pregnancy mass were considered. The size of the gestational sac was obtained from medical records, and patients without reported sacs were excluded.

Patient details, pregnancy and medical history, treatment methods, clinical and demographic information, and laboratory findings including TSH, fT3, fT4, TT3, TT4, Thyroglobulin, Anti-thyroglobulin Antibody, TSH receptor antibody (TrAB), Anti-Peroxidase Antibody, Anti-Thyroglobulin Antibody, hemogram, biochemistry, CRP, and sedimentation were recorded. Pregnant women using drugs for thyroid dysfunction, with a history of ectopic pregnancy or tubal surgery, were excluded from both groups. (Figure 1)

**Statistical Analysis:** In our study, we determined the sample size by conducting a power analysis, considering the prevalence of ectopic pregnancy (1-2%) and thyroid diseases (5-10%), study power (95%), and significance level (5%). To detect a significant difference, we used the following formula to measure the difference between two independent groups: $n = 2(Z_{\alpha/2} + Z_{\beta})^2 * \sigma^2 / (X_1 - X_2)^2$. Based on these calculations, we initially planned to work with 40 patients. To anticipate patient losses, we aimed to increase the initial sample size. Although the sample size was adjusted to account for potential dropouts, the final analysis was conducted with 31 patients.

Statistical analyses were performed using IBM® SPSS® 26 (SPSS Inc., Chicago, IL, USA) program. The conformity of variables to normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were given as mean±std. deviation. Descriptive statistics were performed by giving frequency (n) and percentage (%) values for categorical variables. Pearson's or Fisher's Exact Chi Square tests were used to compare categorical variables. t test or Mann-Whitney U test was used to compare continuous data

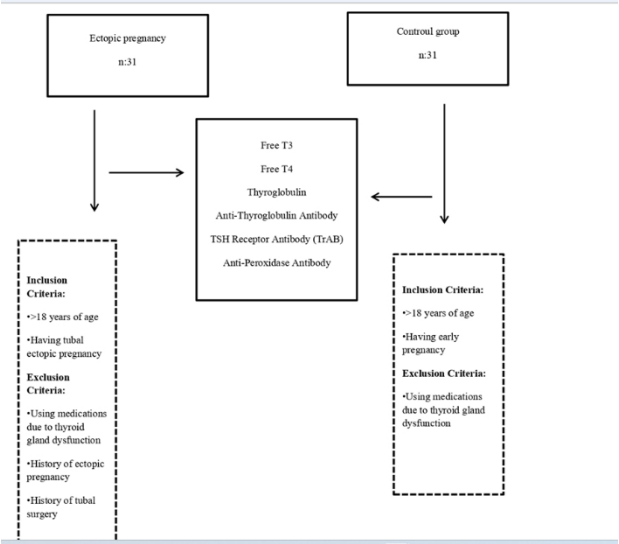


**Fig. 1.** Flow Diagram

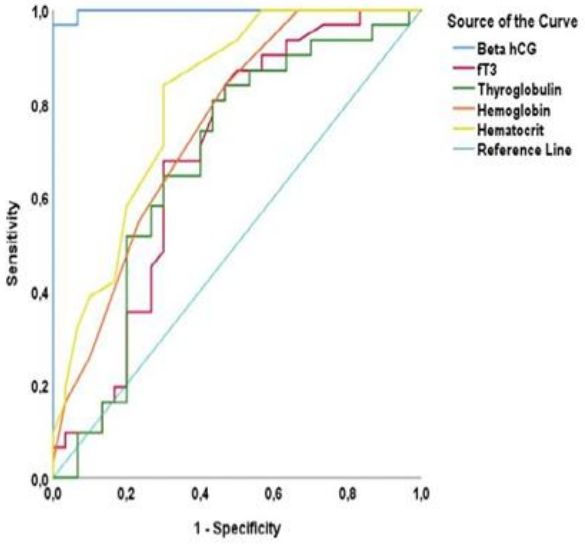


**Fig. 2.** ROC analysis for determining predictive parameters for to distinguish patientsfrom control groups

type between the control and patient groups. ROC analysis was applied to determine predictive parameters to distinguish the patient group. Multivariate logistic regression analysis was used to determine risk parameters. Cases where the p-value was below 0.05 were considered statistically significant.

## Results

Biochemical and hematological parameters were subjected to a comparative analysis between the patient and control groups. The patient group exhibited significantly lower levels of β-hCG, fT3, Thyroglobulin, Hemoglobin, and hematocrit parameters (refer to Table 1). Within the ectopic pregnancy group, 13 patients underwent medical treatment, while 17 patients underwent surgical intervention.

To assess the disease state, ROC analysis was conducted using the significant parameters from Table 1. The analysis yielded AUC (Lower and Upper Bound), sensitivity, specificity, and cut-off values for each parameter.(Figure 2)Consequently, distinguishing between patients with β-hCG below 13,580, fT3 at 3.22, thyroglobulin value of 24.2, hemoglobin level of 11.5, and hematocrit below 37.5 may prove useful. However, a comprehensive multivariate perspective that considers both significant and other biochemical parameters for ectopic pregnancy diagnosis is warranted.

Upon reviewing Table 2, the need for a multivariate approach is discussed in Table 3, where multivariate logistic regression analysis was applied to identify and assess risk parameters. In this evaluation, three different steps and models were developed. In the initial model, all biochemical parameters related to the diagnosis of ectopic pregnancy were considered, but none of the parameters proved statistically significant and, therefore, could not be included in the model.

In the second step, a "backward stepwise model" was employed to predict which other thyroid-biochemical diagnostic parameters might accompany the fT3 parameter. Only fT3 could be included in the model alone (p=0.017). Similar to the second step, the apparent parameter that increased the risk of the disease was fT3, showing a 4.2-fold increase with a 95% CI of [1.3-13.5].

In summary, a comprehensive analysis suggests that fT3 plays a significant role in predicting the risk of ectopic pregnancy when considering thyroid-biochemical diagnostic parameters

## Discussion

Mendez et al. investigated conducted a study investigating the effects impact of hypothyroidism on different tubal regions and showed that hypothyroidism increased the number of, revealing an increase in intraepithelial lymphocytes in the fimbria/infundibulum, and increased elevated levels of triacylglycerol content, oxidized lipids, and glycogen content in the ampulla, isthmus, and utero-

**Table 1:** Comparison of Biochemical and Hematological Parameters Among Patient and Control Groups

| Variables | Control (n=31) | Patient (n=30) | p value |
|---|---|---|---|
| | Mean±SD | Median (IQR) | |
| Age, (years) | 29.8±4.6 | 31.6±5.6 | 0.174 |
| Parity (n) | 2.8±1.1 | 2.8±2.1 | 0.145 |
| BMI, n (%) | 26.3±4.7 | 25.8±3.1 | 0.679 |
| Gestational week | 6.4 ±1.4 | 6.5±1.7 | 0.568 |
| Staying Hospital (Days) | 0±0 | 2.6±0.7 | 0.0001 |
| β-hCG | 65699(49026) | 2194(3005) | 0.001* |
| Free T3(ng/L) | 3.4±0.4 | 3.1±0.6 | 0.011 |
| Free T4(ng/L) | 1.2±0.2 | 1.1±0.2 | 0.095 |
| Thyroglobulin | 29.4(29.4) | 15.9(20.8) | 0.018* |
| TSH | 1.4(1.6) | 1.7(1.4) | 0.078* |
| Anti-Thyroglobulin Antibody | 0.4(0.8) | 0.4(1.1) | 0.459* |
| TSH Receptor Antibody (TrAB) | 0.37(0.47) | 0.33(0.32) | 0.954* |
| Anti-Peroxidase Antibody | 49.7(24.5) | 45.5(27.1) | 0.498* |
| WBC , (K/uL) | 8.7±2.4 | 8.2±2.2 | 0.460 |
| Lymphocyte, % | 24±5.9 | 25.7±7.7 | 0.345 |
| Neutrophil, % | 69±6.6 | 66.5±9.8 | 0.234 |
| Hemoglobine g/dl; | 12.8±1.4 | 11.4±1.6 | 0.001 |
| Hematocrit g/dl; | 39.7±3.5 | 34.5±4.6 | 0.001 |
| Platelet (K/uL) | 277.1±55 | 260.1±65.7 | 0.276 |
| Glucose (mg/dL) | 98.6±19.3 | 112.7±40.9 | 0.089 |
| Urea (mg/dL) | 21.1±5.4 | 21.6±4.9 | 0.705 |
| Creatinine (mg/dL) | 0.6±0.1 | 0.7±0.2 | 0.436 |
| AST ( U/L) | 17.7±4.4 | 19.5±7.7 | 0.265 |
| ALT ( U/L) | 18.8±9.9 | 15.5±6.1 | 0.121 |
| Sedimentation (mm/hr) | 26.5±11.9 | 23.8±12.9 | 0.242* |
| CRP, mg/dL | 6.2±5.8 | 6.8±7.7 | 0.884 |

Independent t test and * Mann-Whitney U test was used.
p<0.05 considered significant. AST: Aspartataminotransferase, ALT: Alanineaminotransferase, CRP: C-reactive protein, White Blood Cell (WBC),BMI: Body Mass Index,TSH: Thyroid Stimulating Hormone WBC: White Blood Cell

tubal junction. They reported their findings suggested that the effect effects of hypothyroidism is probably related are likely linked to the different distinct physiological functions specific to each region (10). On the other hand Additionally, it has been suggested proposed that sphingolipid metabolism in the fallopian tube may play a role in ectopic pregnancy by resulting with impaired sphingolipid metabolism via, influenced by Thyroid hormone-sensitive protein (THRSP) ), may contribute to ectopic pregnancy (14,15).

In our study, thyroid function tests, including Free T3, Free T4, Thyroglobulin, and TSH, were conducted in both groups.i Free T3 and Thyroglobulin levels were notably lower in the ectopic pregnancy group than in compared to the control group. The differences in Free T3 (p = 0.011) and thyroglobulin (p = 0.018) values were statistically significant. Subsequently, ROC analysis was performed for the significant parameters, and determining AUC (Lower and Upper Bound), sensitivity, specificity, and cut-off values were determined for each parameter. Multivariate logistic regression analysis was then performed. Conducted. In the next stage subsequent step, the “"backward stepwise model”" was applied to the Free T3 parameter, and 4.2 times revealing a 4.2-fold increase

**Table 2:** Determining The Estimated Values of The Parameters To Distinguish Patients From Control Groups

| Test Result Variable(s) | AUC | Std. Error | p Value | AUC 95% Confidence Interval | | Sensitivity (%) | Specificity (%) | Cut-off Value (<) |
|---|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | | |
| β-hCG | 0.998 | 0.003 | 0.0001 | 0.992 | 1.000 | 93.3 | 100 | 13580 |
| Free T3 | 0.687 | 0.070 | 0.012 | 0.549 | 0.825 | 70 | 67.7 | 3.22 |
| Thyroglobulin | 0.676 | 0.072 | 0.018 | 0.536 | 0.817 | 73.3 | 58.1 | 24.24 |
| Hemoglobin | 0.750 | 0.062 | 0.001 | 0.628 | 0.872 | 53.3 | 83.9 | 11.5 |
| Hematocrit | 0.808 | 0.056 | 0.0001 | 0.699 | 0.918 | 70 | 71 | 37.5 |

ROC (Receiver operating characteristic) analysis was used and p<0.05 considered significant.
AUC; Area under curve

**Table 3:** Multivariate analysis to determine biochemicalrisk parameters

| Model | Variables | B | S.E. | Wald | df | p value | Exp(B) | OR | 95% C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Lower | Upper |
| Step 1a | Free T3 | -1,29 | 0,7 | 3,2 | 1 | 0,074 | 0,275 | 3,6 | 0,9 | 15,0 |
| | Free T4 | -1,43 | 1,9 | 0,6 | 1 | 0,445 | 0,240 | 4,2 | 0,1 | 161,6 |
| | Thyroglobulin | -0,01 | 0,0 | 0,8 | 1 | 0,372 | 0,990 | 1,0 | 1,0 | 1,0 |
| | TSH | 0,30 | 0,3 | 1,2 | 1 | 0,264 | 1,353 | 1,4 | 0,4 | 1,3 |
| | Anti-Thyroglobulin Antibody | -0,12 | 0,1 | 1,7 | 1 | 0,193 | 0,885 | 1,1 | 0,9 | 1,4 |
| | TSH reseptör antikor (TrAB) | 0,87 | 0,9 | 1,0 | 1 | 0,324 | 2,381 | 2,4 | 0,1 | 2,4 |
| | Anti-Peroxidaz Antibody | 0,00 | 0,0 | 0,0 | 1 | 0,824 | 1,002 | 1,0 | 1,0 | 1,0 |
| | Constant | 5,27 | 2,7 | 3,8 | 1 | 0,053 | 194,5 | | | |
| Step 2b | Free T3 | -1,44 | 0,6 | 5,6 | 1 | 0,018 | 0,238 | 4,2 | 1,3 | 13,9 |
| | Thyroglobulin | -0,01 | 0,0 | 1,2 | 1 | 0,283 | 0,989 | 1,0 | 1,0 | 1,0 |
| | Constant | 4,95 | 2,0 | 5,9 | 1 | 0,015 | 140,727 | | | |
| Step 3c | Free T3 | -1,43 | 0,6 | 5,7 | 1 | 0,017 | 0,239 | 4,2 | 1,3 | 13,5 |
| | Constant | 4,58 | 2,0 | 5,5 | 1 | 0,019 | 97,762 | | | |

*Logistic regression analysis was used and p<0.05 considered significant.*
*a &b; Enter method, c; Backward stepwise method, CI; Confidence Interval, OR; Odds Ratio*

with a 95% CI of [1.3-13.5] was as the apparent parameter in which the associated with an elevated risk increased in of the disease. Decreased Free T3 levels are associated were identified as being correlated with an increased risk of ectopic pregnancy.

Thyroid hormones exert their influence on the uterus and fallopian tube by interacting with intracellular receptors and modulating the response of these organs to estrogen (16). The expression of T3 and T4 receptors in the uterine epithelium peaks in reaches its peak during the middle of the secretory phase, whereas while the expression of deiodinases decreases in the secretory this phase and is, inversely proportional to correlated with the increase rise in progesterone. It has been reported studies indicate that type 3 deiodinase, which is particularly important crucial in fetal and placental tissues, is upregulated experiences upregulation during decasualization in the presence of thyroid hormones, and. Furthermore, the progesterone receptor plays a role is implicated in the decision-making caused processes influenced by thyroid hormones (17,18). Therefore, it is plausible that changes in Consequently, alterations in serum T3 and T4 serum levels affect uterine and fallopian tube may impact the morph physiology of the uterus and fallopian tube in the genital tract by affecting the. This influence may extend to receptors and plasma

concentrations of sex steroids during estrus or the menstrual cycle (19,20).

In the uterine tube, similar to the changes observed changes in the uterus, a deficiency of thyroid hormones significantly reduces diminishes the epithelial height of that segment by reducing. This reduction occurs by affecting the height of the villi of the infundibulum as well as the number and size of the cells lining the villus (21). All of these changes modifications in the uterus and uterine tubes can have the potential to compromise crucial processes such as fertilization, differentiation, nutrition, and embryo implantation (22,23).

Akram et al.. investigated . conducted an investigation on thyroid-related proteins in different parts various segments of the fallopian tube. They stated that emphasized the presence significance of thyroid-related proteins in the fallopian tube and the improvement enhancement of embryo development after with T4 treatment, underscoring the importance of a functional thyroid system, is important for a normal pregnancy (24). Öner et al. stated supported this perspective, asserting that the presence of Thyroid Hormone Receptors (THR) in the uterus and fallopian tubes is an designates these organs as active region of sites for thyroid hormones in these organs (9).

Hatsuta et al. stated reported that in mice with decreased T3 levels after medical, whether induced medically or through surgery, experienced decreased FSH and LH levels decreased, and , coupled with an increase in progesterone levels increased (25). Palitieli et al. reported that suggested a connection between high progesterone levels cause, ciliary dysfunction, and may subsequently cause the potential for subsequent ectopic pregnancy (26). Goldman et al. reported found that while T3 had no effect impact on basal progesterone secretion but, it inhibited hCG-induced steroid secretion (27). The effects of thyroid hormones on the reproductive system are complex intricate and reciprocal.

In our study, it was possible to have an effect the potential impact on the risk of ectopic pregnancy due to was explored, considering its effects influence on ciliary dysfunction and, tubal motility due to decreased free T3 levels, and its effect on progesterone.

In our study, no statistical there was no statistically significant difference was observed in the comparison of auto-antibodies, such as Anti-Thyroglobulin Antibody, TSH Receptor Antibody (TrAB), and Anti-Peroxidase Antibody, between the two groups.

Thyroid autoimmunity is stands as the leading primary cause of thyroid dysfunction in among women of reproductive ages. Women with thyroid autoimmunity have been reported are known to be at a higher face an elevated risk for of adverse reproductive outcomes, including miscarriage and premature birth, even if they have normal when their thyroid function is within the normal range (28,29). Hosotani et al. stated suggested that such autoimmune diseases, manifesting morphological changes in the infundibulum in the across systemic and reproductive organs of autoimmune diseases also cause changes, can induce alterations in ciliary motility.

Rahnama et al. reported that the expression of thyroid peroxidase (TPO) expression is mainly primarily localized in glandular and luminal epithelial cells in the endometrium, and that. They found an association between TPO expression in the endometrium and placenta is associated with and a higher frequency of abortion and infertility in patients with thyroid autoimmunity (30). Geva et al. measured conducted a study measuring antithyroid autoantibodies in 40 patients with unexplained infertility and 40 patients with tubal obstruction infertility They concluded that antithyroid autoantibodies could be the cause of a causative factor in both unexplained and tubal infertility (31). In contrast, Turhan et al. reported significant differences in Th1- and Th17-related cytokine levels in the first trimester in pregnant patients with thyroid autoimmunity, which may have potentially impacting reproductive results outcomes (32). According to a study by Tim et al.., TPOAb-positive women with low FT4 levels relative to their hCG levels are at a higher risk of preterm delivery. They stated suggested that TPOAb positivity may might lead to negative pregnancy outcomes through changes alterations in gestational thyroid function (33). Kagan et al. found that serum β-HCG levels in early pregnancy were lower in thyroid patients were lower in patients with thyroid autoimmunity than in compared to those without thyroid autoimmunity (34).

Over the past decades, accumulating growing body of evidence has shown that highlighted the intricate interplay between thyroid and reproductive hormones, including estrogen, progesterone, glucocorticoids, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and oxytocin.

Thyroid hormones regulate exert their regulatory effects on the behavioral and physiological effects aspects of reproductive hormones by binding to intracellular thyroid hormone receptors, hormonal receptors, or membrane receptors and activating gene networks. As a result of these The complex interactions, result in thyroid hormones interfere with influencing synthesis and secretion, affect affecting

other hormones, and even affect modulating hormonal balance. Therefore, they are among the most important factors involved As a consequence, thyroid hormones emerge as crucial players not only in the regulation of female reproductive processes but also in the emergence development of hormone-related diseases. More however, further studies are needed imperative, as the underlying molecular mechanisms are not yet fully remain incompletely understood. The Unraveling the interaction between thyroid and reproductive hormones, elucidating secondary structural changes, and elucidation of understanding the underlying mechanisms will contribute to the understanding of comprehending the etiology of female reproductive diseases and will provide, offering new insights, and presenting opportunities for the treatment of gynecological diseases. (35).

One limitation of our study is the relatively small number of included patients, which should be duly acknowledged in the limitations section. The inclusion of a limited number of patients in our study may partially restrict the generalizability of our results. Future research with a larger patient sample is warranted to validate our findings and achieve more comprehensive results. Additionally, it should be noted that histopathological examination of the thyroid and fallopian tubes could not be performed.
The strengths of our study are that it is lie in being the first prospective study to examine investigate the relationship between ectopic pregnancy and thyroid.

Ectopic pregnancies are an important cause of stand as a significant contributor to maternal mortality and morbidity worldwide. Negative on a global scale, with well-established negative reproductive outcomes are well known. The effects of interactions between thyroid hormones on and the reproductive system are reciprocal intricate and complex, bidirectional. In our study, we observed an association between low Free T3 levels were associated with and an increased elevated risk of ectopic pregnancy. Monitoring Free T3 levels before pregnancy may help in the early detection and prevention of ectopic pregnancies. Pregnancies. However, as it is essential to note that our study is, being the first of its kind at the clinical level, necessitates further research and validation through additional studies are needed for a more comprehensive understanding.

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