



Study of the relationship between thyroid hormones and liver functions and infertility in women

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Abstract

Background: Female infertility is linked to hypothyroidism, with the liver playing a crucial role in thyroid hormone metabolism. This study aimed to investigate the impact of thyroid disorders on liver function and their connection to female infertility.

Materials and Method: The study involved 55 infertile women as the test group and 30 non-infertile women as a control group, all aged 18-46, from a private clinical laboratory in Mosul. Blood samples were collected for serum biochemical tests measuring T3, T4, TSH, AST, ALT, and ALK-PH levels. Data analysis included statistical tests such as arithmetic mean, standard deviation, Mann-Whitney U-Test, and linear correlation coefficients.

Results: Findings revealed elevated levels of T4 (43.47), TSH (58), and AST (43.07) at a significance level of 0.05. Conversely, T3 (28.22), ALT (43.19), and ALK-PH (37.15) showed lower values at the same significance level. Total serum bilirubin (TSB) did not exhibit significant differences but showed an inverse relationship with TSH, T4, and T3 levels.

Conclusion: The study concludes that infertility is a complex condition influenced by hormonal imbalances and thyroid disorders, potentially leading to various gynecological issues such as menstrual irregularities and infertility.

Keywords: Thyroid disorders, hypothyroidism, liver enzymes, infertility

Introduction

Infertility is defined as the inability of a couple to conceive naturally after (12) months of unintended intercourse or seeking to achieve pregnancy, due to health problems suffered by one or both spouses (Gerhid, & Guillermina, 2020)^[11]. It is classified into:

Primary Infertility occurs in women whose pregnancy is subject to spontaneous abortion or leads to their pregnancy to give birth to a dead child without having a live birth (Al-Turki, *et al.*, 2015)^[4].

Secondary Infertility: occurs in women who are subject to permanent early miscarriage or continue their pregnancy to give birth to a dead fetus after a previous pregnancy or previous ability to carry the pregnancy to a live birth (Narjes, & Tina, & Meimanat, 2017)^[22].

There are many causes of infertility in women in general, such as endocrine disorders, biological and enzymatic disorders that affect reproduction, and ovulation in females (Zina, Zahraa, & Mousa, 2016)^[29], as well as important factors in the causes of infertility damage, the woman's age, the month of May, such as preeclampsia and ovarian, as well as the patient, the third and third, wants nutrition, alcohol, smoking, and is no longer present, and chronic diseases such as liver disease completely, and does not need blood pressure, and the specific device cannot be. (Lynch, *et al.*, 2014)^[19]. Infertility is a global problem for people in all societies, although the causes do not differ according to geographical location and social and health status (Elhussein, *et al.*, 2019)^[9].

According to the global health index, the prevalence of infertility is (1.9%) among women aged (20-44), and it is estimated that 60-80 million individuals are infertile alone (Chehreh, *et al.*, 2019)^[5], and the global prevalence of breast cancer in women aged (20-45) years continues, and the incidence of roughness is increasing worldwide (Silva, Ocarino, & Serakides, 2018)^[25]. Endocrine diseases are the most common diseases among women of reproductive age,

and therefore the evaluation of lymph node functions that cause infertility and some related diseases becomes very important (Roya, *et al.*, 2021)^[24].

Thyroid hormones are essential for the functioning of the female reproductive system because they regulate metabolism, the development of ovarian, uterine and placental tissues, so hypothyroidism and hyperthyroidism can lead to infertility or sterility in women (Alexander, *et al.*, 2017)^[2]. Thyroid hormones are involved in the regulation of various physiological processes, so changes in their concentrations can damage the proper functioning of the organism. Thyroid dysfunction leads to menstrual cycle disorders, ovulation cycles, and decreased fertility in women of reproductive age (Krassas, & Markou, 2019)^[15].

The aim of this study was to evaluate its role and not yet determined on infertility in women by performing liquidity TSB, TSH, T3 and some specialties such as enzymes AIK.Ph. Alk.AST is important in evaluating the causes of patients with liver dysfunction, which can be considered a biochemical marker for many diseases.

Materials and Method

Study design and setting

Total number of infertile and non-infertile women (85) women of reproductive age, aged between (18-46) years, number of infertile women (patients) (55) women, and non-infertile women (controls) (30) women, who attended clinical local private laboratory, where their consent was obtained to take the necessary samples for the study and to participate voluntarily in this study, and the ages of infertile and non-infertile women were taken into account. The biochemical variables required for this study such as hormonal and enzymatic tests, T3, T4, TSH, AST, ALK.ph, TSB, were measured in infertile and non-infertile women

Sample size and sampling technique

Blood samples were collected from infertile and non-

infertile women, and placed in plastic tubes without anticoagulant. and leave it for (10) minutes to coagulate, then put the tubes in the centrifuge for (15) minutes at (3000) revolutions per minute, In order to obtain the largest amount of serum, it must be free of any traces of red blood cells.and the blood must not be decomposed, then the serum is drawn using a micropipette and placed in plastic tubes and frozen 20C for the purpose of using them in biochemical tests (Corica, *et al.*, 1996)^[7].

Measuring thyroid hormone levels

Serum concentration is measured TSH, T4, T3, Using measurement AFIAS Test and using a device AFIAS (Felig, & Frohman, 2001)^[10].

AFIAS Test It is a fluorescent immunoassay and is useful in the management and monitoring of thyroid disorders (Clinial Guide to Laboratory Test, 2006)^[6], and in the laboratory diagnosis of serum and plasma was used Colorimetric method to measure serum concentration levels in AST (Kikwood, 1988)^[14], ALT (Mazin, Karar, & Ali, 2024)^[21], ALK.ph (Laurence, and Carole, 2002)^[17]. As for measuring the bilirubin concentration TSB, the serum concentration level was measured according to the method Sulfanilic Acid Method (Corica, *et al.*, 1996)^[7].

Ethical Consideration

This study adhered to strict ethical guidelines to ensure the protection of patient rights and data confidentiality. All patient information was obtained from a local private laboratory with full compliance with ethical and legal

standards.

Prior to data collection, informed consent was obtained from all participants after they were fully briefed on the study’s purpose, procedures, risks, and benefits. To protect privacy, patient data were anonymized and de-identified, ensuring that no personally identifiable information was disclosed. The study received approval from the relevant ethical review board to ensure adherence to research ethics by the local clinical laboratory letter no. 4345 on 13 October 2023.

Data analysis

The Shapiro-Wilk normal distribution test was used in the statistical analysis of the results with a probability significance of (0.05), and the non-parametric test (Mann-Whitney U test) was used to compare independent samples with a probability significance of (0.05), and to find the relationship between the biochemical variables, the linear correlation coefficient was used with a probability significance of (0.05), (Kikwood, 1988)^[14].

Results

As shown in Table (1), according to the statistical indicators represented by the arithmetic mean and standard deviation, the results showed a decrease in the concentration of the T3 hormone in infertile women (44.00) compared to non-infertile women (control) (46.00) which appeared less than (0.05), while an increase in the concentration of the T4 hormone, TSH, appeared in infertile women (150.32), (12.13) compared to non-infertile women (control).

Table 1: Biochemical concentrations in infertile women compared to healthy women (arithmetic mean ± standard deviation).

Case Summaries									
Sample Type	Statistic Index	Age	T3	T4	TSH	AST	ALT	Alk.ph.	TSB
Control	N	30	30	30	30	30	30	30	30
	Mean	31.73	2.35	99.67	2.56	21.07	19.00	57.37	0.54
	Std.	7.98	0.53	23.44	1.08	4.93	7.73	16.01	0.28
	Min.	18.00	1.33	68.87	0.74	13.00	8.00	33.00	0.10
	Max.	44.00	3.10	140.21	4.02	31.00	35.00	90.00	1.10
Patient	N	55.00	55.00	55.00	55.00	55.00	55.00	55.00	55.00
	Mean	32.98	0.93	102.43	9.14	21.22	19.15	46.25	0.55
	Std.	6.25	0.29	26.62	1.13	5.81	7.41	13.56	0.23
	Min.	20.00	0.38	66.77	7.16	12.00	7.00	18.00	0.10
	Max.	46.00	2.01	150.32	12.13	32.00	34.00	73.00	1.10

The levels of Alk.ph,ALT enzymes decreased in infertile women (73.00) (34.00) compared to non-infertile women (control) (90.00) (35.00), and the level of enzyme AST showed an increase in infertile women (32.00) compared to non-infertile women (control) (31.00), while there were no

significant differences between infertile and non-infertile women (control) in the level of TSH concentration (1.10) (1.10). Table (2) shows the results for all tests in (Shapiro-Wilk) test (P-value) appeared less than (0.05).

Table 2: Biochemical Varibales according to the (Shapiro-Wilk) test in infertile and healthy women:

Tests	Sample type	Tests of Normality		
		Shapiro-Wilk		
		Statistic	Df	P-value
T3	Control	.917	30	.022
	Patients	.951	55	.026
T4	Control	.893	30	.006
	Patients	.903	55	.000
TSH	Control	.913	30	.017
	Patients	.978	55	.402
AST	Control	.960	30	.307
	Patients	.935	55	.005
ALT	Control	.939	30	.035
	Patients	.959	55	.028

Alk.ph.	Control	.943	30	.007
	Patients	.977	55	.376
TSB	Control	.962	30	.352
	Patients	.945	55	.014

The (Mann-Whitney U Test) was used to compare between women with primary infertility and women with secondary infertility, as the results in Table (3) indicated in all tests (TSB,Alk.ph,ALT,AST,TSH,T4,T3) in terms of the

probability value that reached (0.694) (0.795) (0.231) (0.788) (0.295) (0.253) respectively, as all values appeared greater than (0.05).

Table 3: Biochemical variables according to the Mann-Whitney U-Test in infertile women according to the type of infertility.

Test	Sample	Mean rank	Statistic	P-value
T3	Primary infertility	29.94	291.0	0.253
	Secondary infertility	24.86		
T4	Primary infertility	29.78	296.5	0.295
	Secondary infertility	25.12		
TSH	Primary infertility	27.54	372.5	0.788
	Secondary infertility	28.74		
AST	Primary infertility	25.97	426.0	0.231
	Secondary infertility	31.29		
ALT	Primary infertility	29.21	316.0	0.477
	Secondary infertility	26.05		
Alk.ph.	Primary infertility	27.56	372.0	0.795
	Secondary infertility	28.71		
TSB	Primary infertility	27.34	379.5	0.694

In terms of the value of the linear correlation coefficient indicate that there is an inverse relationship between TSB and TSH, T4, T3 (-0.157), (-0.162), (-0.114), Table (4). However, this relationship is not statistically significant, as indicated by the probability value associated with the linear correlation coefficient, which was (0.252, (0.236), (0.406), which is greater than (0.05).

Table 4: The relationship between (TSB), (T3), (T4), and (TSH) in infertile women.

Correlation				
		T3	T4	TSH
TSB	Pearson Correlation	-.114	-.162	-.157
	P-value	.406	.236	.252
	N	55	55	55

** . Correlation is significant at the 0.01 level (2-tailed).

The results of Table (5) show an inverse relationship between TSB and Alk.ph, AST as shown by the linear correlation coefficient. (-0.036), (-0.070).

Table 5: The relationship between (TSB), (AST), and (Alk.ph) in infertile women

Correlations				
		AST	ALT	Alk.ph.
TSB	Pearson Correlation	-.070	.166	-.036
	P-value	.611	.224	.794
	N	55	55	55

However, this relationship is not statistically significant, as indicated by the probability value associated with the linear correlation coefficient (0.744), (0.611) which is greater than (0.05). There was also a direct relationship between (TSB) and (ALT) in terms of the value of the linear correlation coefficient (0.166) which is not significant in terms of the probability value of the linear correlation coefficient (0.224) which is greater than (0.05).

Discussion

The results of the study conducted on (55) infertile women showed a decrease in the T3 hormone and an increase in the TSH and T4 hormones in infertile women compared to non-infertile women (control). The results also showed an increase in the concentration of the AST enzyme and a decrease in the concentration of the ALK.Ph and ALT enzymes in infertile women compared to non-infertile women (control), and there were no significant differences in the concentration of TSB between infertility women and non-infertile women and between women with primary infertility and women with secondary infertility in all biochemical variables (T3, T4, TSH, AST, ALT, ALK.ph, TSB). The results of the linear correlation coefficient indicated an inverse relationship between TSB and T3, T4, TSH and a direct relationship between TSB and ALT, while there was no relationship between TSB and AST, ALK.ph. Increased or decreased levels of thyroid hormones can lead to an imbalance in reproductive hormones, and thyroid and undiagnosed diseases may be a cause of infertility. The result of low T3 is consistent with what was mentioned by (Kris, 2021) [16], as the reason for the low T3 hormone in infertile women is due to the fact that thyroid hormones have a direct effect on granulosa cells, yellow cells, and egg maturation and indicated (Sudha, & Reddy, 2017) [26] that low T3 hormone leads to hypothyroidism, hyperthyroidism, pituitary or hypothalamic hyperfunction, menstrual disorders, anovulation, and infertility. Also, high levels of TSH and T4 hormones in women with infertility due to thyroid disorders and changes in the thickness of the uterine lining, and thus the inability to conceive, and this is consistent with what mentioned by (Lawal, et al., 2020) [18]. He mentioned (Zhao, et al., 2018) [28] that high TSH indirectly affects FSH receptors, which is an indicator for assessing thyroid function, and that its increased concentration leads to thyroid dysfunction, hypogonadism, failure to maintain the fertilized egg, recurrent pregnancy loss, decreased ovarian function, and

thus weak fertility. There is a great harmony between thyroid hormones and reproductive hormones secreted by the pituitary gland. The increase and decrease in thyroid hormones affects reproductive hormones (Alexander, *et al.*, 2017)^[2].

The liver plays an important role in the metabolism, digestion, detoxification and elimination of substances in the body (Mangione, *et al.*, 2023)^[20]. The results increase in the AST enzyme, indicates liver cell damage or other diseases such as heart disease and hypothyroidism. These results are consistent with (Khansaa, Al-Salih, & Saher, 2017)^[13]. The AST enzyme is present in high concentrations in the liver, and in many other organs such as the heart, pancreatic cells, and nerve cells (Al-Hilali, Al-Samarrai, & Al-Bdri, 2018)^[3].

ALT enzyme decrease does not match what was mentioned (Elhussein, *et al.*, 2019)^[9], and the reason for the decrease may be due to a malfunction in liver functions resulting from liver diseases that lead to weak ovulation due to weak metabolism of the hormone progesterone, and due to obesity and insulin resistance. ALT enzyme is considered an indicator of hyperandrogenism and is a cytoplasmic enzyme that is present in high concentrations in the liver and in small quantities in tissues and kidneys (Krassas, & Markou, 2019)^[15]. A decrease in the concentration of the enzyme ALK.ph is due to the occurrence of reproductive gland disorders due to infertility, hypothyroidism, and other diseases such as polycystic ovary syndrome and reproductive gland tumors, as the enzyme ALK.ph is considered an indicator of liver and bone diseases, and many studies have confirmed its role in thyroid diseases, endocrine diseases, and adrenal gland disorders (Reghavendra, *et al.*, 2022)^[23]. In this study, there were no significant differences between infertile and non-infertile women (control). The occurrence of changes in liver enzymes leads to a dysfunction in liver function and metabolism, which is reflected in progesterone metabolism (Valdés, *et al.*, 2017)^[27]. As Roya *et al.* mentioned, poor progesterone metabolism causes weak ovulation resulting from liver dysfunction and liver disease (Roya, *et al.*, 2021)^[24]. Infertility, whether primary or secondary, is due to female-related causes such as fallopian tube problems, miscarriage, ovulation disorders, age, chronic diseases, and genetic factors (Silva, Ocarino, & Serakides, 2018)^[25]. There were no significant differences between primary and secondary infertility in women with infertility in all biochemical tests. Primary or secondary infertility can be emotionally and physically challenging, but there are many options for success (Narjes, Tina, & Meimanat, 2017)^[22].

The result of the inverse relationship between TSB and TSH is consistent with (Laurence, & carole, 2002)^[17] mention the inverse relationship that bilirubin levels in infertile females are associated with thyroid disorders that lead to hormonal disorders and decreased fertility, and that the change in thyroid levels occurs with an increase in bilirubin (John & Damodara, 2022)^[12].

The direct relationship between TSB and ALT indicates that the association between bilirubin and liver enzymes is useful for assessing liver diseases, and bilirubin causes liver dysfunction and affects enzyme levels, according to researchers (Alexander, *et al.*, 2017)^[2]; Aldhalimi, & Aldujaili, 2023)^[1]. There is no relationship between TSB and ALK.ph, AST and this results consistent with (Mazin, Karar, & Ali, 2024)^[21] which indicated that bilirubin level is

inversely related to risk factors for metabolic syndrome, menopausal status, body mass index (BMI) and C-reactive protein.

Conclusions

The present study revealed that the relative risk of female infertility was significantly increased in women with hypothyroidism. Thyroid dysfunction causes menstrual and ovulation disorders, leading to infertility. Thyroid hormones play an important role in normal reproductive function through direct effects on the ovaries and also indirectly through multiple interactions with sex hormones. Biochemical changes can also affect infertility. Therefore, thyroid hormone testing should be considered in all women with a female cause of infertility so that patients can be diagnosed and treated with medications or other medical treatments. The causes of infertility, whether primary or secondary, are not a problem specific to women, but rather both women and men contribute to infertility. It is necessary to increase women's awareness of the factors causing infertility, to pay attention to reproductive health, and to spread health culture among women to avoid the risk of infertility.

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