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The prevalence of hypothyroidism in infertile women and its correlation with the pituitary gland hormones

Ali S. Al-khafaji
Department of medical laboratory Technology, College of health and medical techniques, Southern Technical University, Basra, Iraq

Abdulkareem M. jewad
Department of medical laboratory Technology, College of health and medical techniques, Southern Technical University, Basra, Iraq.
Corresponding author email: drkreem.mohammed@stu.edu.iq

***Abstract*---**Infertility is defined as a condition in which a woman cannot conceive after 12 months of a normal sexual relationship without the use of contraception. The study aimed to evaluate hypothyroidism prevalence, thyroid and pituitary gland hormones assessment in infertile women's serum, and their correlation in Basra, Iraq. The research was conducted at Ibn-Gzouan Hospital for Obstetrics and Gynecology in Basra, southern Iraq, between October 2021 and March 2022. In our research, 28 infertile women with hypothyroidism, 30 infertile women without hypothyroidism, and 30 fertile women aged 18 to 45 were studied. Our research found that infertile hypothyroid women had greater TSH and PRL levels than fertile women, but lower T3 and T4 levels. Without hypothyroidism, infertile women exhibited greater PRL, cortisol, and LH levels than fertile women, but lower IGF-1 levels. T4 and T3 levels (r=0.640), LH, and LH/FSH ratio(r=0.536) correlated positively in hypothyroid infertile women. TSH and T4 levels (r = -0.514) and FSH and LH/FSH ratio (r =-0.481) correlated negatively. T4 and T3 levels, LH, and LH/FSH were positively correlated (r = 0.666) in infertile women without hypothyroidism. TSH was negatively correlated with T4 (r = -0.547) and T3 (r = -0.580).

***Keywords*---**Female Infertility, Hypothyroidism, PCOS, TSH, LH/FSH ratio.

1. Introduction

Females are four to five times as likely as males to have thyroid problems. Hormone and androgen metabolism, menstrual function, and fertility are all affected by hyperthyroidism and hypothyroidism. (Talwar, 2012).Hypothyroidism affects 2% to 4% of women in their reproductive years (Lincoln, 1999). They can lead to puberty being delayed, menstrual irregularities, anovulatory cycles, miscarriages, and infertility (Unisa, 1998; Zargar et al., 1997). A thyroid disorder, if left untreated, can result in both subfertility and infertility. Any female who had more than two abortions or is unable to conceive after a year of unprotected intercourse and has a family history of thyroid problems or an irregular menstrual cycle has undergone more than two abortions. An evaluation of her thyroid is necessary. (TSH) levels in the blood can be used to detect hypothyroidism quickly. Subclinical hypothyroidism is defined as low T3 and T4 levels with a minor increase in TSH levels, whereas clinical hypothyroidism is defined as high TSH levels with low T3 and T4. Increased (PRL) amount and delayed LH response to GnRH are frequently related to Hypothyroidism resulting in elevated levels of thyrotropin-releasing hormones (Akter et al., 2020). Even if PRL levels are elevated, To determine the cause of high PRL levels, medication should be administered first to correct hypothyroidism (Stamatiades et al., 2019). Hypothyroidism, characterized as an unusually increased Concentration of TSH in people of reproductive age, affects 2 to 4% of the population (Bjoro et al., 2000; Strieder et al., 2003). Age and dietary iodine status are two factors that may influence spread. Autoimmune thyroid disease is most prevalent due to hypothyroidism in procreative women and thyroid peroxidase antibodies are identified in most patients (Hollowell et al., 2002; M. P.J. Vanderpump et al., 1995). Drug-induced hypothyroidism can also occur after thyroiditis. Hypothyroidism is linked to many reproductive issues, including aberrant sexual development, menstruation abnormalities, and infertility. Hypothyroidism causes a delay in sexual maturity in the first ten years of life. Early adolescence, galactorrhea, and latency in pubic hair development indicate juvenile hypothyroidism. Thyroid hormone supplementation helps to reverse these symptoms. More prevalent ovulatory problems in adult women have been observed; galactorrhea, hirsutism, amenorrhea, and menorrhagia are some conditions that might affect women (Poppe & Velkeniers, 2004). Since 1950, hypothyroidism has been linked to changes in the course of the menstrual cycle adult women with hypothyroidism frequently experience changes in cycle duration and blood flow (Ajmani et al., 2016). Menorrhagia (expanded bloodstream) was the most widely recognized indication in more established investigations, occurring in 60% of overt (GOLDSMITH et al., 1952). Krassas found that menstruation abnormalities were detected in 23.4 percent of 171 hypothyroid patients, much more significant than 8% found in 214 normal participants in a more recent study. Furthermore, oligomenorrhea was the most common symptom. Amenorrhea was seen in just 12% of hypothyroid patients. None of the participants was used as a comparison. Thyroid illness was discovered sooner in the Greek review, one of the most likely explanations for the disparities. According to Krassas' research, increased TSH was associated with more menstrual irregularities (Krassas et al., 1999).

2. Aim of the study

The study aimed to evaluate hypothyroidism prevalence in infertile women, thyroid and pituitary gland hormones assessment in infertile women's serum, and their correlation in Basra, Iraq.

3. Subjects and methods

3.1. Subjects:

It is a case-control study of 88 women; 28 infertile women with hypothyroidism, 30 infertile women without hypothyroidism, and 30 fertile women. The participants were aged 18 to 45 years old, and they visited the infertility and IVF center in Ibn-Gzouan Hospital for Obstetrics and Gynecology in Basra, southern Iraq, between October 2021 and December 2022.

3.2. Methods:

Each participant (patients and controls) had five milliliters of human blood drawn, and transferred to sterilized test tubes, for 30 minutes at room temperature to allow it to coagulate. After centrifuging a blood sample for ten minutes at 3000 rpm, the serum was then isolated and kept at -20 degrees Celsius. The serum was then isolated into an Eppendorf tube and used for measuring the concentration of TSH, T3, T4, PRL, cortisol, estradiol, FSH, and LH by Cobas e 411 kits and measuring the concentration of GH and IGF-1 by Sunlong Chania Elisa kits.

3.3 Ethical Consideration

The study protocol was approved by the ethical research committee of Health and Medical Techniques College/ Southern Technical University. In addition, verbal approval was taken from all participants and controls.

4. Statistical Analysis

Data are stated as means ± standard deviation (SD). Differences between groups' means were tested by t-test, and chi-square test. Correlations between variables were also determined. All statistical analyses were performed using SPSS for Windows (version 25, USA). Non-parametric Kruskal-Wallis test was done and Mann Whitney test was also applied when the normal distribution is not met. For the normal distribution, use one-way ANOVA. A value of $P < 0.05$ was considered statistically significant and $P > 0.05$ non-significant.

5. Results

Our study included 28 infertile women with hypothyroidism and 30 infertile women without hypothyroidism and 30 fertile women. The results of our study revealed as follows:
Table (1) reveals there's a non-significant difference ($p > 0.05$) between the Fertile group and the Infertile group in terms of age, and duration. BMI measurement

shows a highly significant increase (P < 0.01), in the infertile women with and without hypothyroidism group compared to the fertile group.

Table (1) Statistical distribution of the study groups by their age, body mass index, and duration

Items	Fertile (N=30)		Inf. with HT (N=28)		Inf. Without HT (N=30)		P value*
	Mean	±SD	Mean	±SD	Mean	±SD	
Age (years)	30.87	6.129	28.61	6.344	28.27	7.575	0.273
Duration (years)			5.11	2.713	6.23	4.125	0.228
BMI (Kg/M^2)	13.97	7.907	25.34	8.021	24.89	9.141	**0.000**

Inf. with HT: infertile with hypothyroidism; Inf. without HT: infertile without hypothyroidism

Our study included women diagnosed with infertility with hypothyroidism and with infertility without hypothyroidism both compared with the Fertile group. We found that the Total number of infertile women that were visited the Infertility and IVF Center in Ibn-Gzouan Hospital for Obstetrics and Gynecology for the period between October 2021 and March 2022 was 302, only 28 (9.21%) of them suffered from hypothyroidism 20 (71.4%) of whom with clinical hypothyroidism and 8 (28.6%) with subclinical hypothyroidism Table (2)

Table (2) The prevalence of hypothyroidism in infertile women in Basra

Total infertile women (N= 304)			
Infertile women with hypothyroidism (N=28) 9.21%			
Clinical Hypothyroidism		Subclinical hypothyroidism	
Freq	%	Freq	%
20	71.4	8	28.6

Table (3) shows the comparison of the thyroid hormone between infertile women with hypothyroidism compared to the fertile group. The results revealed that there is a highly significant increase in thyroid-stimulating hormone level (TSH) (p< 0.01), and a highly significant decrease in levels of triiodothyronine (T3) and thyroxine (T4) (p<0.01) compared to the fertile group.

Table: (3): A comparison between fertile and infertile women in the hypothyroidism group

Group	Fertile		Infertile with hypothyroidism		P value*
parameters	Mean	± SD	Mean	± SD	
T3 (nmol/L)	1.767	0.399	0.776	0.241	**0.0000**
T4 (nmol/L)	102.5	30.42	47.30	12.27	**0.0000**
TSH (µIU/L)	1.919	0.830	7.173	3.767	**0.0000**

Table (4) shows the comparison of the thyroid hormone between infertile women without hypothyroidism compared to the fertile group. The results revealed that

Group	Fertile		Infertile without hypothyroidism		P value*
Parameters	Mean	±SD	Mean	±SD	
T3 (nmol/L)	1.767	0.399	2.365	1.197	**0.044**
T4 (nmol/L)	102.5	30.42	121.9	43.63	0.121
TSH (µIU/L)	1.919	0.830	1.450	0.963	0.284

There is a significant increase in Triiodothyronine (T3) ($p<0.05$), and a non-significant difference ($P >0.05$) in the TSH and T4 levels in the infertile women without hypothyroidism group compared to the fertile group.

Table: (4): A comparison between fertile and infertile women without hypothyroidism group

When the hormone levels of fertile and infertile women with hypothyroidism were examined, the statistical differences in prolactin, cortisol, LH, and IGF-1 levels, as well as the measurement of LH/FSH, were found to be extremely significant, as shown in Table (5)

Table: (5): A comparison of hormone levels between fertile and infertile with hypothyroidism group

Groups	Fertile		Infertile with hypothyroidism		P-value*
Parameters	Mean	±SD	Mean	±SD	
PRL (ng/dl)	18.54	6.500	40.33	21.80	**0.0001**
E2 (pg/mL)	176.0	66.53	181.5	62.81	0.534
Cortisol(nmol/L)	137.1	27.01	242.8	115.3	**0.001**
FSH (mIU/mL)	6.210	1.790	5.798	1.814	0.657
LH (mIU/mL)	3.852	1.178	5.215	2.128	**0.004**
IGF-1 (ng/ml)	5.031	3.864	3.475	1.450	**0.014**
GH (pg/ml)	317.5	93.75	341.0	125.4	0.250
LH/FSH (mIU/mL)	0.624	0.096	0.947	0.414	**0.0001**

By comparing the hormone levels between fertile and infertile without hypothyroidism groups as in Table (6) it is clear that there is a significant difference in the levels of the same hormones and LH/FSH measurement as in Table (5).

Table (6): A Comparison of hormone levels between fertile and infertile without hypothyroidism groups

Group	Fertile		Infertile without hypothyroidism		P-value*
Parameter	Mean	±SD	Mean	±SD	
PRL (ng/dl)	18.54	6.500	45.46	20.97	**0.0001**
E2(pg/mL)	176.0	66.53	177.4	44.75	0.442

Cortisol(nmol/L)	137.1	27.01	291.1	142.1	**0.0001**
FSH (mIU/mL)	6.210	1.790	5.461	1.591	0.214
LH (mIU/mL)	3.852	1.178	6.676	2.168	**0.0001**
IGF-1 (ng/ml)	5.031	3.864	3.487	1.826	**0.001**
GH (pg/ml)	317.5	93.75	330.6	64.17	0.101
LH/FSH (mIU/mL)	0.624	0.096	1.313	0.519	**0.0001**

The correlation between the study parameters (BMI, TSH, T3, T4, PRL, FSH, LH, Cortisol, E2, GH, IGF-1, and LH/FSH) in infertile women with hypothyroidism as in Table (7) showed that:

1- There were statistically significant positive correlations between BMI measurement and cortisol level, T4 level and T3 level, T4 level and IGF1, and between cortisol level and LH/FSH measurement, LH and LH/FSH measurement.

2- There were statistically significant negative correlations between BMI measurement and FSH level; TSH level and T4 level; TSH level and IGF1 level; FSH level and cortisol level; and between FSH level and LH/FSH measurement.

Table (7): Spearman's correlations between basic and hormonal quantitative variables in the infertile with hypothyroidism group

Infertile women with hypothyroidism (N=28)												
Category		**TSH**	**T4**	**T3**	**PRL**	**FSH**	**LH**	**E2**	**Cortiso 1**	**GH**	**IGF1**	**LH/FSH**
BMI	R	.245	-.348-	-.224-	-.131-	**-.414-**	.015	-.049-	**.496**	.036	-.133-	.256
	Sig.	.208	.070	.252	.505	**.029**	.942	.806	**.007**	.855	.501	.189
TSH	R		**-.514-**	-.242-	-.058-	-.302-	-.162-	-.013-	-.092-	.084	**-.456-**	.170
	Sig.		**.005**	.214	.768	.119	.410	.948	.641	.670	**.015**	.387
T4	R			**.640**	-.135-	.138	-.146-	.178	-.114-	-.086-	**.429**	-.131-
	Sig.			**.000**	.493	.485	.459	.364	.564	.664	**.023**	.506
T3	R				.042	.322	-.112-	.143	-.257-	-.032-	.274	-.223-
	Sig.				.831	.095	.570	.467	.187	.871	.158	.253
PRL	R					.113	.055	-.229-	.139	.020	-.009-	-.045-
	Sig.					.568	.780	.242	.480	.919	.963	.818
FSH	R						.353	-.304-	**-.387-**	.040	.036	**-.481-****
	Sig.						.066	.116	**.042**	.839	.856	**.010**
LH	R							-.199-	.353	.071	-.308-	**.536****
	Sig.							.311	.066	.718	.111	**.003**
E2	R								-.098-	-.132-	.084	.188
	Sig.								.619	.502	.673	.339
Cortiso 1	R									.033	-.091-	**.597****
	Sig.									.866	.645	**.001**
GH	R										-.113-	-.037-
	Sig.										.569	.852
IGF1	R											-.312-
	Sig.											.106

The correlation between the study parameters (BMI, TSH, T3, T4, PRL, FSH, LH, Cortisol, E2, GH, IGF-1, and LH/FSH) in infertile women without hypothyroidism as in Table (8) showed that:

1- There were statistically significant positive correlations between BMI measurement and cortisol level, T4 and T3 level, LH level, and LH/FSH measurement.
2- There were statistically significant negative correlations between TSH level and T4 level, TSH and T3 level, TSH level and IGF1 level, prolactin level and growth hormone, prolactin level and IGF1, FSH and cortisol, FSH and LH/FSH measurement.

Table (8): Spearman's correlations between basic and hormonal quantitative variables in the infertile without hypothyroidism group

Infertile without hypothyroidism women (N=30)												
Category		**TSH**	**T4**	**T3**	**PRL**	**FSH**	**LH**	**E2**	**Cortisol**	**GH**	**IGF1**	**LH/FSH**
BMI	R	.149	-.023	-.163-	-.006	-.146	.233	-.004	**.621**	.140	.045	.288
	Sig.	.433	.903	.390	.977	.440	.215	.982	**.000**	.460	.812	.122
TSH	R		**-.547**	**-.580**	.262	-.143	.149	.068	.164	-.096-	**-.419-**	.247
	Sig.		**.002**	**.001**	.162	.450	.432	.720	.387	.613	**.021**	.188
T4	R			**.666**	-.293-	.039	-.171-	-.174-	-.190-	.190	.249	-.142-
	Sig.			**.000**	.117	.836	.365	.358	.314	.314	.184	.453
T3	R				-.034-	.201	-.076-	-.116-	-.183-	.091	.139	-.246-
	Sig.				.858	.288	.689	.543	.334	.632	.462	.190
PRL	R					-.123-	.283	.080	.223	**-.464-**	**-.396-**	.250
	Sig.					.517	.130	.673	.237	**.010**	**.030**	.183
FSH	R						.117	-.075-	**-.387-**	.213	-.104-	**-.733-****
	Sig.						.539	.695	**.035**	.258	.585	**.000**
LH	R							.061	-.001-	.200	.171	**.501****
	Sig.							.749	.996	.290	.368	**.005**
E2	R								.060	-.115-	.317	.132
	Sig.								.753	.546	.088	.486
Cortisol	R									-.069-	-.217-	.358
	Sig.									.716	.249	.052
GH	R										.310	-.009-
	Sig.										.095	.961
IGF1	R											.177
	Sig.											.351

6. Discussion

Hypothyroidism is associated with decreased thermogenesis, decreased metabolic rate, and has also been shown to correlate with a higher body mass index (BMI) and a higher prevalence of obesity. There is clinical evidence suggesting that even mild thyroid dysfunction in the form of subclinical hypothyroidism is linked to significant changes in body weight and represents a risk factor for overweight and obesity (Sanyal & Raychaudhuri, 2016).

T3 and T4 levels was a highly significant decrease in the infertile women in the hypothyroidism group compared to the fertile group ($P < 0.01$), while TSH levels show a highly significant increase ($P < 0.01$). The results of our study were in agreement with previously reported studies of several types of research as in the following:

A study by Sridevi and Sandhya Rani, (2015) was found when comparison of clinical hypothyroid cases with controls. Serum T3 and T4 levels were found to be significantly decreased and serum TSH levels were found to be significantly increased in clinical hypothyroid women compared to controls. thyroid dysfunction was present in 53% of infertile women. It is obvious from the observation that the fertility of the women's reproductive system is hampered by altered thyroid hormone levels (Sridevi & Sandhya Rani, 2015). hypothyroidism was found in 24%-28% of women with primary and secondary infertility. In hypothyroidism, increased thyrotropin-releasing hormone (TRH) production stimulates both TSH and prolactin secretion and that leads to hyperprolactinemia and altered gonadotropin-releasing hormone (GnRH) secretion (Bari et al., 2020). Hypothyroidism may occur as a result of primary gland failure or insufficient thyroid gland stimulation by the hypothalamus or pituitary gland. Autoimmune thyroid disease is the most common etiology of hypothyroidism in the United States (Gaitonde et al., 2012). Iodine deficiency is the most common cause of hypothyroidism worldwide. (Mark P.J. Vanderpump & Tunbridge, 2002).

In infertile women without hypothyroidism, serum T3 levels showed a significant increase ($P < 0.05$) compared to the fertile group. This elevation is within the normal range, and the difference in value may be due to the small sample size of our study. TSH and T4 levels show no non-significant difference compared to the fertile group.

The prolactin level shows a highly significant increase in infertile women with hypothyroidism compared to fertile women. Our results concurred with the research of (Yadav et al., 2014); (Hussein et al., 2019); (Bhandari et al., 2019); (Bari et al., 2020). A study done by Yadav (2014), found women with hypothyroidism had significantly high serum prolactin levels as compared to controls. Low serum levels of thyroxine (T4) would decrease negative feedback on the hypothalamopituitary axis resulting in increased secretion of thyrotropin-releasing hormone (TRH). TRH stimulates thyrotropes as well as lactotrophs, thereby increasing the levels of both thyroid-stimulating hormone (TSH) and prolactin (Yadav et al., 2014).

The cortisol hormone levels result reflect a highly significant increase in infertile women with hypothyroidism compared to the fertile group, our results agree with the documented studies (Siriwardhane et al., 2019);(Kebapcilar et al., 2014);(Isabirye et al., 2012);(Zina L. Hassan, 2016). Hypothyroidism induces obesity, stress, anxiety, and depression, thus cumulatively causing inflammation in the body, which leads to difficulty in conception, frequent miscarriages, and infertility in severe cases. Chronic psychological and physical stress is common among hypothyroid individuals, this causes an elevated production of cortisol (Isabirye et al., 2012).

The results reveal a highly significant increase ($p < 0.01$) in the level of LH in infertile women with hypothyroidism compared to the fertile group. The current results are consistent with each result (Sarma, 2015); (Levavi-Sivan et al., 2010); (Elslimani et al., 2016). According to research by Sarma (2015), hypothyroid infertile women had elevated levels of prolactin and LH but normal FSH, suggesting their vulnerability to developing polycystic ovary syndrome. The current research also implies that the altered hormonal state of gonadotropins may contribute to the irregular menstrual cycle and predispose hypothyroid women to polycystic ovarian syndrome (Sarma, 2015).

Measurement of LH/FSH was found to be a highly significant increase ($P < 0.001$) in infertile women with hypothyroidism compared to fertile women. Our study agrees with (Elslimani et al., 2016); (Chandan K. Nath et al., 2017); and (Yu & Wang, 2016). According to the findings of Yu, 2016 which was reported that PCOS combined with subclinical hypothyroidism has a highly significant increase in LH/FSH ratio in SCH PCOS compared to euthyroid control (Yu & Wang, 2016).

Prolactin levels were highly significant increase in the infertile women without hypothyroidism compared to the fertile group. Our findings concord with other studies by (Filho et al., 2007); (Dehghan et al., 2021);(Newey et al., 2013);(Soni et al., 2018);(Delcour et al., 2019) and (Dehghan et al., 2021). Several possible reasons for Hyper-PRL have been reported in previous studies, among these reasons, Stimulants such as thyrotropin-releasing hormone, vasoactive intestinal peptide, estrogen, and dopamine receptor antagonists induce prolactin secretion (Goyal & Ganie, 2018).

IGF-1 level showed a highly significant decrease in infertile women without hypothyroidism compared to fertile women, these findings disagree with the finding of (Abd El Aal et al., 2005);(Kebapcilar et al., 2014), and (Magdi A. Laban, Tarek A. Shemais, 2018). A study by Kebapcilar (2014) found that there was a highly significant increase in IGF-I levels in women with PCOS subjects concerning the controls (Kebapcilar et al., 2014). On the other hand, our results agree with those of Rashad (2020), who showed a lower level of IGF-1 and IGFBP-3 was found in obese women compared with lean ones. Even more importantly, obese women with depression had significantly lower IGF-1 and IGFBP-3 than those without depression. Early prediction of depression among obese women decreases morbidity (Nearmeen M. Rashada, Ahmed F. Gomaaa, Hanan M. Sabryb & Amira A. Fouadc, 2020).

7. Conclusion

From the results of this study, we concluded that:

a) Among 302 infertile women only 28 (9.21%) of them suffered from hypothyroidism 20 (71.4%) of whom with clinical hypothyroidism and 8 (28.6%) with subclinical hypothyroidism.
b) Body mass index is highly increased in infertile women ($P= 0.000$) and may be a principal cause of infertility.
c) Serum PRL, cortisol, and LH levels as well as LH/FSH ratio significantly increased in infertile women with hypothyroidism and without

hypothyroidism compared to the fertile group, whereas IGF-1 level decreased significantly.

d) Serum E2 and GH hormone levels insignificantly increased, while serum FSH hormone levels insignificantly decreased in infertile women with and without hypothyroidism compared to the fertile group.
e) There was a positive correlation between BMI and cortisol level, T4 and T3 levels, in infertile women with and without hypothyroidism. While T4 and IGF-1 levels and cortisol levels and LH/FSH ratio were in infertile women with hypothyroidism.
f) There was a negative correlation between TSH and T4 levels, FSH and cortisol levels, and FSH and LH/FSH ratio in infertile women with and without hypothyroidism, while TSH and T3 levels, PRL and GH levels, and between PRL and IGF-1 levels were only infertile women without hypothyroidism. On the other hand, there was a negative correlation between BMI and FSH levels in infertile women with hypothyroidism.

8. Conflicts of interest

We, the authors, declare that we have no conflict of interest.

9. Acknowledgments

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