

## **INVESTIGATION OF THYROIDS DYSFUNCTION AMONG INFERTILE WOMEN IN NASIRIYAH CITY**

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### **ABSTRACT**

**Objective:** Epidemiological studies revealed that 10-15 % of couples in the world experience infertility. Thyroid dysfunction (hyperthyroidism and hypothyroidism) possessed adverse effect on reproductive health and resulted in, interference with ovulation, reduced rates of conception, increased early pregnancy loss, and adverse effects on pregnancy and neonatal outcomes. The current study aims to explore the thyroid dysfunction among infertile women in Nasiriyah city-Iraq.

**Methods:** The study was conducted on 60 infertile women (age group 17–45 y) who visited infertility departments in Al-Hussein hospital, Al-Haboubi hospital and Bent AL Huda hospital, in Nasiriyah city, from October 2019 to March 2020. Thirty normal females (age matched) were taken as controls. TSH, T3, T4, LH, FSH, prolactin, progesterone and estradiol levels were determine by using VIDAS® Assay.

**Results:** The prevalence of hyperthyroidism among infertile women was 13.33% and hypothyroidism was 10.00%. Both hyper and hypothyroidism induced adverse changes in the serum levels of LH, FSH, prolactin and gonadal hormones.

**Conclusion:** Thyroid dysfunction was associated with a risk of not getting pregnancy. Women were advised to achieve euthyroidism before planning a pregnancy.

**Keywords:** Thyroid dysfunction, Hyperthyroidism, Hypothyroidism, Infertile, Women

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### **INTRODUCTION**

Infertility is the inability to conceive after one year of regular intercourse without contraception [1]. Epidemiological studies revealed that 10-15 % of couples in the world experience infertility [2]. Thyroid dysfunction (hyperthyroidism and hypothyroidism) possessed adverse effect on reproductive health and resulted in, interference with ovulation, reduced rates of conception, increased early pregnancy loss, and adverse effects on pregnancy and neonatal outcomes [3]. The incidence of both clinical and subclinical hyperthyroidism was 2.3% of infertile women, compared with an incidence of 1.5% of women in the general population [4, 5]. Many studies showed that the prevalence of thyrotoxicosis, of which Graves' disease was presumably the most frequent, was 0.4% in the United States, 0.6% in Italy and 1.1-1.6% in the United Kingdom [6, 7]. Treatment of thyroid disorders, and maintaining of the thyroid-stimulating hormone level at the normal level, improved conception rates and reduce early pregnancy loss [3, 8]. Thyroid dysfunction can affected female fertility from different ways included hormonal effect [9-12], abnormalities of menstrual cycle [13-17], effect on ovary function and ovulation [15, 18-22] and adverse effects on pregnancy [15, 19, 23-26]. The current study aims to explore the thyroid dysfunction among infertile women.

### **MATERIALS AND METHODS**

The study was conducted on 60 infertile women (age group 17–45 y) who visited infertility departments in Al-Hussein hospital, Al-Haboubi hospital and Bent AL Huda hospital, in Nasiriyah city, from October 2019 to March 2020. Thirty normal females (age matched) were taken as controls. Infertile women (sexually active, not using contraception, and not lactating, who trying for a pregnancy for one years or more). Patients with tubal factors infertility, polycystic ovary syndrome, endometriosis, urogenital tract anomalies, pelvic inflammatory disease, under thyroid disorders or hyperprolactinemia treatments, diabetic, hypertensive and patients with hepatic, cardiovascular and renal diseases were excluded. Patients with abnormal husband's semen analysis were also excluded. The study was approved by the

ethical committee of the postgraduate studies of Southern Technical University-Basrah, and performed after taking informed, written consent of the participants [27].

A questionnaire was prepared for each patient to obtain the following information: age, residence, duration of marriage, infertility history (primary, secondary infertility) and duration of infertility [28].

Venous blood (5 ml) was aseptically collected from the infertile and fertile women by venipuncture during the same period in the menstrual cycle (luteal phase) and dispensed into plain bottles (gel tube), allowed to clot, retracted and centrifuged (5000 RPM) for 5 min. The serum obtained was separated and frozen till used for determination of TSH, T3, T4, LH, FSH, prolactin, progesterone and estradiol. Hormonal assays were carried out using VIDAS® Assay.

The statistical analysis was carried out using student-t-test.

### **RESULTS**

#### **Incidence of hyper and hypothyroidism among infertile women**

The prevalence of hyperthyroidism among infertile women was 13.33% (8 of 60 patients) and hypothyroidism was 10.00% (6 of 60 patients), while 76.67% (46 of 60 patients) showed a normally functioning thyroid gland. Of euthyroid patients, 6 (13.04%) complained low gonadotropines, 12 (26.08%) with hyperprolactinemia and 28 (60.87%) showed normal gonadotropines and gonadal hormones levels (table 1).

#### **Characteristics of patients with thyroid dysfunction among infertile women**

50% of the infertile women with hyperthyroidism were from rural areas and 50 % from the urban areas, while 83.33% of the infertile women with hypothyroidism were from rural areas and 16.67% from the urban areas. Of euthyroid infertile women 43.33% from the rural areas and 56.67% from urban areas. Primary infertility was recorded in 50, 16.67 and 33.33% of the infertile women with

hyperthyroidism, hypothyroidism and euthyroid infertile women, respectively. The mean duration of infertility was 4.87 and 9.25 and

7.63 y in infertile women with hyperthyroidism, hypothyroidism and euthyroid infertile women respectively.

**Table 1: Prevalence of hyper and hypothyroidism among infertile women**

Groups			Number	Percent
Infertile women	Euthyroid	Low gonadotropines	6 (13.04% of Euthyroid)	46 76.67%
		Hyperprolactenemia	12 (26.08% of Euthyroid)	
		Normal gonadotropines and prolactin levels	28 (60.87% of Euthyroid)	
	Hyperthyroid	8	13.33%	
	Hypothyroid	6	10.00%	

**Correlation between TSH, thyroid hormones and gonadotropines, prolactin and gonadal hormones**

Infertile women with hyperthyroidism showed low levels of both serum LH 4.482±1.3 mIU/ml (P<0.05) and FSH 4.971±2.4 mIU/ml (P<0.01) compared with control values of LH 5.281±2.3 mIU/ml and FSH 6.703±2.5 mIU/ml, while, infertile women with hypothyroidism showed normal FSH 6.385±3.3 mIU/ml and significantly declined serum LH level 3.451±1.7 mIU/ml (P<0.01). On the other hand, hormonal analysis of euthyroid infertile women with low gonadotropines levels revealed highly significant declined levels of both LH 0.731±1.6 mIU/ml (P<0.001) and FSH levels 1.328±2.6 mIU/ml (P<0.001). Euthyroid infertile women with hyperprolactinemia showed mild decline of both LH 4.395±1.1 mIU/ml (P<0.05) and FSH levels 5.495±2.4 mIU/ml (P<0.05). However, only serum LH in euthyroid infertile women with normal gonadotropines and prolactin levels, was declined 4.644±1.0 mIU/ml (P<0.05), while FSH level was in the normal limit 6.385±3.3 mIU/ml compared with control 6.703±2.5 mIU/ml. Infertile women with hyperthyroidism showed significantly higher prolactin level 23.555±4.1 ng/ml (P<0.05), while infertile women with hypothyroidism showed normal prolactin levels 19.238±3.6 ng/ml compared with control group 18.500±4.5 ng/ml. In the infertile

women with euthyroid, the prolactin level was only elevated significantly in the subgroup of euthyroid with hyperprolactinemia 38.107±7.5 ng/ml (P<0.001), while subgroups euthyroid infertile women with low gonadotropines and normal gonadotropines and prolactin levels showed normal prolactin levels 18.500±4.5 ng/ml and 16.511±3.1 ng/ml respectively compared with control 18.500±4.5 ng/ml. The infertile women with hyperthyroidism and the infertile women with hypothyroidism showed normal serum progesterone level 0.696±0.3 ng/ml and 0.765±0.3 ng/ml, but significantly declined estradiol (E2) level 63.312±13.1 pg/ml (P<0.01) and 53.193±14.5 pg/ml (P<0.01) respectively, compared with control 83.513±12.1 pg/ml. Progesterone and estradiol (E2) analysis of euthyroid infertile women with low gonadotropines revealed normal estradiol (E2) level 83.600±214.3 pg/ml and significantly declined progesterone levels 1.097±0.2 ng/ml (P<0.05) compared with control 0.636±0.2 ng/ml. However, euthyroid infertile women with hyperprolactinemia showed significantly low serum levels of estradiol (E2) 75.103±13.4 pg/ml (P<0.05), and progesterone level 1.000±0.1 ng/ml (P<0.05), while, euthyroid infertile women with normal serum gonadotropines and prolactin levels showed normal progesterone level 0.816±0.2 ng/ml and significantly declined estradiol (E2) level of 62.088±11.6 pg/ml (P<0.1) (table 2).

**Table 2: Hormonal analysis of the infertile women**

Groups		TSH mIU/ml	T3 nmol/l	T4 nmol/l	LH mIU/ml	FSH mIU/ml	Prolactin ng/ml	Progesterone ng/ml	Estradiol (E2) pg/ml	
Control		1.882±0.9 <sup>a</sup>	1.340±0.2	88.144±8.9	5.281±2.3	6.703±2.5	18.500±4.5	0.636±0.2 <sup>a</sup>	83.513±12.1 <sup>a</sup>	
Infertile women	Euthyroid	Low gonadotropines	2.8217±1.2 <sup>a</sup>	1.513±0.3 <sup>a</sup>	82.458±10.6 <sup>a</sup>	0.731±1.6 <sup>b</sup>	1.328±2.6 <sup>b</sup>	16.071±3.4 <sup>a</sup>	1.097±0.2 <sup>b</sup>	83.600±14.3 <sup>a</sup>
		Hyperprolactinemia	2.068±1.3 <sup>a</sup>	1.666±0.4 <sup>b</sup>	85.848±9.5 <sup>a</sup>	4.395±1.1 <sup>c</sup>	5.495±2.4 <sup>c</sup>	38.107±7.5 <sup>b</sup>	1.000±0.1 <sup>b</sup>	75.103±13.4 <sup>b</sup>
		Normal gonadotropines and prolactin levels	1.862±0.9 <sup>a</sup>	1.485±0.3 <sup>a</sup>	88.854±8.9 <sup>a</sup>	4.644±1.0 <sup>c</sup>	6.465±2.6 <sup>a</sup>	16.511±3.1 <sup>a</sup>	0.816±0.2 <sup>a</sup>	62.088±11.6 <sup>c</sup>
	Hyperthyroid 8 of 60	0.606±0.2 <sup>b</sup>	1.601±0.2 <sup>b</sup>	88.553±9.1 <sup>a</sup>	4.482±1.3 <sup>c</sup>	4.971±2.4 <sup>c</sup>	23.555±4.1 <sup>c</sup>	0.696±0.3 <sup>a</sup>	63.312±13.1 <sup>c</sup>	
	Hypothyroid 6 of 60	5.545±1.8 <sup>c</sup>	1.093±0.2 <sup>c</sup>	75.878±12.4 <sup>b</sup>	3.451±1.7 <sup>c</sup>	6.385±3.3 <sup>a</sup>	19.238±3.6 <sup>a</sup>	0.765±0.3 <sup>a</sup>	53.193±14.5 <sup>d</sup>	

Vertically, different letter means significant variations; the P value was mentioned in the text.

**DISCUSSION**

Thyroid hormones play critical roles in growth, differentiation and metabolism. They are important for optimal functioning of almost all tissues with major effects on metabolic rate and oxygen consumption. Thyroid dysfunctions interfere with female reproductive performance. Several studies highlighted the association of hyperthyroidism or hypothyroidism with hormonal disturbances, anovulatory cycles, decreased fecundity and increased lost of pregnancy [15, 17, 29].

The current study aims to investigate the prevalence of thyroid dysfunction among infertile women. Measurement of thyroid hormones, especially thyroid stimulating hormone, was considered as an important component of infertility work up in women [30].

Serum TSH showed a log-linear relationship to thyroxin. The assay of TSH was commonly used as the most sensitive test to detect minor degrees of primary thyroid hormone abnormalities [31].

The study showed that the incidence of hyperthyroidism among infertile women was 13.33% (8 of 60 patients) and hypothyroidism was 10.00% (6 of 60 patients), while 76.67% (46 of 60 patients) showed normally functioning thyroid gland. However, many previous studied mentioned that hyperthyroidism is thought to be found in 2.3% of women with subfertility, compared with an prevalence of 1.5% of women in the general population [4, 5]. The prevalence of thyrotoxicosis was 0.4% in the United States, 0.6% in Italy and 1.1-1.6% in the United Kingdom [6, 7]. The high prevalence of thyroid dysfunction in this study in comparison with the mentioned studies could be attributed to general high prevalence of hyperthyroidism in the studied population [32, 33].

In addition, the previous studied deal with clinical cases only, while in this study we included all the clinical and subclinical hypo and hyperthyroidism cases. However, the majority of the tested infertile women in our study showed normal thyroid function (76.67%). These results were in agreement with Goswami et al., who found

that the majority of the infertile women were euthyroid. In infertile group, the prevalence of thyroid dysfunction was slightly higher than that of the general population [20].

Our study revealed that TSH level in infertile women with hyperthyroidism was significantly lower ( $0.606 \pm 0.2$ ), while, significantly higher in infertile women with hypothyroidism ( $5.545 \pm 1.8$ ) than in control group ( $1.882 \pm 0.9$ ). Correlation of prolactin level with thyroid function showed that hyperthyroidism (but not hypothyroidism) associated with significantly higher level of prolactin,  $23.555 \pm 4.1$  ( $P < 0.05$ ).

These results were in agreement with many studies, showed that serum prolactin was significantly ( $P < 0.05$ ) higher in infertile group with thyroid dysfunction compared with control [9, 20, 34].

Many previous studies revealed that there was a positive correlation between serum TSH and prolactin levels in the infertile subjects. Hyperprolactinemia was depicted in 41% of the infertile women while it was only 15% in the control group. The infertile women with hypothyroidism had significantly higher prolactin levels when compared to the subjects with hyper-or euthyroidism [9, 20].

TRH regulated the levels of cytoplasmic prolactin mRNAs in a line of functional rat pituitary cells. Prolactin mRNA increased from 1.1 to 4.5% within 48 h after addition of TRH to the medium) suggested that TRH was responsible for the stimulation of prolactin mRNA levels [35, 36].

Our study showed declined level of LH, FSH and estradiol (E2) levels in the infertile women with hypothyroidism, hyperthyroidism and hyperprolactinemia. These data in agreement with Liu *et al.*, who found that the serum levels of gonadotropin releasing hormone (GnRH) and follicle stimulating hormone (FSH) in both hypo-and hyperthyroidism rat models were significantly decreased on the luteal phase, although there were no significant changes at earlier time points. There were no significant differences in luteinizing hormone (LH) or progesterone levels between the treatment and the control groups [9].

These effects could be attributed to the elevated level of prolactin in the infertile women with hyperprolactinemia and hypo and hyperthyroidism.

It is well documented that hyperprolactinemia interferes with the female reproductive function, the mechanism by which hyperprolactinemia interferes with the normal hypothalamic-pituitary-ovarian axis, leading to menstrual abnormalities and anovulation. Hyperprolactinemia interferes at hypothalamic level with the GnRH release; this was suggested by studies showing failure of estrogen to elicit a positive feedback on gonadotropines secretion; however other studies showed diminished fluctuation pattern of LH secretion. Hyperprolactinemia may also act at the pituitary level by desensitizing it to GnRH effect and decreases FSH and LH release from anterior pituitary. Hyperprolactinemia also possesses direct effect of on the ovaries and interferes with steroidogenesis [37].

## CONCLUSION

The prevalence of hyperthyroidism among infertile women was 13.33% and hypothyroidism was 10.00%. Both hyper and hypothyroidism induced adverse changes in the serum levels of LH, FSH, prolactin and gonadal hormones. Thyroid dysfunction was associated with a risk of not getting pregnancy. Women were advised to achieve euthyroidism before planning a pregnancy.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

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