Original Article

Hormones level in Primary and Secondary Iraqi Infertile Women: Comparative Study

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Abstract

Background: Infertility is a worldwide health problem that can be categorised into two types: primary infertility, which refers to women who have never been able to get pregnant, and secondary infertility, which is the inability to conceive after a prior pregnancy. **Material and Methods:** The research was carried out at Al-Ramadi Teaching Hospital for Women and Children in Anbar, Iraq, spanning from August 23, 2023, to December 31, 2023.This study comprised a total of 90 samples, consisting of 60 women diagnosed with infertility (30 with main infertility and 30 with secondary infertility). Additionally, 30 healthy women were included as a control group.All individuals aged between 18 and 45 years old. The hormonal analysis was conducted using the MAGLUMI® X3 Snibe diagnosis, which utilises the Fully-auto Chemiluminescence Immunoassay (CLIA) System. **Aims:** The objective is to evaluate the blood hormone levels between women with primary infertility and those with secondary infertility, as well as to examine the association among these hormones. **Results:** The present study demonstrated that women with primary and secondary infertility exhibited significantly higher mean levels of FSH, LH, T3, T4, and prolactin in their blood serum compared to fertile women. Conversely, women with primary and secondary infertility had the lowest levels of estradiol hormone in their blood serum compared to fertile women. Furthermore, the study revealed a substantial positive link between follicle-stimulating hormone (FSH) and luteinizing hormone (LH), triiodothyronine (T3), thyroxine (T4), and prolactin. Conversely, there was a negative correlation between FSH and estradiol (E2). The study found a strong positive association between LH and T3, T4. Additionally, the research reveals a negative association between thyroid-stimulating hormone (TSH) and estradiol (E2). A recent study has revealed that T3 exhibits a positive correlation with T4, whereas it shows a negative correlation with E2. Additionally, T4 demonstrates a substantial negative correlation with E2. Conclusion: There is no significant difference in the levels of reproductive hormones and thyroid hormones between the serum of women with primary infertility and women with secondary infertility.

Keywords: Primary Female Infertility, Secondary Female Infertility, FSH, LH, Thyroid Hormones, E2, Prolactin.

Introduction

Infertility is a substantial worldwide health concern that impacts around 48.5 million couples.[1] Infertility is defined as the failure to conceive a pregnancy following 12 months of consistently engaging in unprotected sexual intercourse.[2] Heart disease and cancer are both frequent ailments, but there is another condition that is even more widespread. It is ranked as the third most prevalent disease globally.[3] This problem can arise due to variables originating from either one or both partners, with a higher prevalence observed in women as a result of factors such as ovulatory disorders, advanced age, substance abuse, and obesity.[1]

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Several reproductive hormones are crucial for the maturation of oocytes, the creation of the corpus luteum, and the preparation of the endometrium for the implantation of a fertilised egg,[4] If any problem arises at the level of the reproductive organs, it can have an impact on fertility. Follicle-stimulating hormone (FSH) is released as a result of gonadotropin-releasing hormone (GnRH) and has a function in the process of sexual maturation and reproduction.[5] The pituitary gland secretes luteinizing

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hormone (LH) in reaction to gonadotropin-releasing hormone (GnRH). It is found in both males and females and plays a role in the development of primary germ cells, as well as promoting the production of oestrogen from the ovaries.[6] It assists in the regulation of the menstrual cycle in females by participating in both the process of ovulation and the implantation of the egg in the uterus.[7] The function of the thyroid gland is linked to infertility. Thyroid hormones, particularly thyroid stimulating hormone (TSH), are recognised as a crucial factor in infertility. TSH is necessary for the generation of estradiol (E2) and progesterone.[8] Fluctuations in Prolactin levels, whether higher or lower than normal, can result in either hyperprolactinemia or hypoprolactinemia, both of which can contribute to infertility.[8]

Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Prolactin (PRL), Thyroxin (T4), and Thyroid Stimulating Hormone (TSH) are hormones that are linked to both primary and secondary infertility. These hormonal factors can serve as reliable diagnostic markers for evaluating the different stages of endometriosis. Fluctuations in the levels of these hormones in the bloodstream can serve as an indicator of certain diseases associated with infertility.[9] The levels of follicle stimulating hormone (FSH) were shown to be lowest in cases of primary infertility (7.66miu/ml) and greatest in cases of secondary infertility (10.5miu/ml).[10] Additionally, in Pakistan, low levels of serum FSH are closely linked to secondary infertility in women who are obese.[3] A study conducted in Kufa City, Iraq revealed a notable and direct relationship between follicle-stimulating hormone (FSH) levels and female infertility. The study observed that as women grow older, their FSH levels tend to rise.[11] Women who are unable to conceive and have polycystic ovaries exhibit elevated average levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) compared to women who are able to conceive.[12]

Oestrogen, in collaboration with follicle-stimulating hormone (FSH), stimulates the pituitary gland to produce more luteinizing hormone (LH). Ovulation is the process in which the egg is released from the ovary due to the shift to LH. Elevated levels of luteinizing hormone (LH) in women may indicate the absence or dysfunction of the ovaries. Elevated levels in a young woman may indicate precocious puberty. Insufficient amounts of luteinizing hormone (LH) in the bloodstream can be indicative of anorexia, pituitary gland dysfunction, stress, or hypothalamic injury in both males and females.[11] Luteinizing hormone (LH) supports theca cells in the ovary, which are responsible for producing androgens and hormone precursors needed for the synthesis of estradiol. The amount of LH is essential for both the process of ovulation and the preservation of luteal function throughout the initial two weeks.[13] Increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) suggest inadequate growth of ovarian follicles, leading to irregular ovulation and malfunction of the ovaries. Conversely, decreased levels of FSH and LH may indicate hyperprolactinemia.[3]

TSH was identified as a crucial diagnostic factor for infertility. Among secondary infertile women with a normal BMI, 18% were discovered to have decreased serum TSH levels. A robust and meaningful positive association was seen between TSH, Age, and BMI. Among women with a normal BMI, an increase in TSH levels was associated with an increase in Gonadotropins level. However, among the overweight population, an increase in TSH levels was linked to a drop in Gonadotropins level.[3] Estradiol is a kind of oestrogen that is synthesised by the ovaries.The elevation of oestrogen hormone levels facilitates the development of the egg and stimulates the growth of the uterine lining. Throughout the menstrual cycle, the concentration of oestrogen hormone gradually increases until it reaches its highest point, triggering a sudden surge in LH concentration around the middle of the cycle. Following a 36-hour rise in LH concentration, ovulation takes place, rendering the egg prepared for fertilization.[14] Prolactin inhibits the hormones FSH and GnRH, which are necessary for ovulation, when its levels increase. Consequently, the generation of gametes and other sexual stimulants is inhibited, thus inhibiting ovulation in women. An absence of ovulation can lead to irregular menstrual periods, ultimately resulting in infertility.[15] Women with primary and secondary infertility had elevated serum prolactin levels compared to fertile women. Increased levels of prolactin hinder the release of Gonadotropin releasing hormone (GnRH) and follicle stimulating hormone, resulting in infertility.[16]

The Aims of Study

are to examine the hormone levels in the blood serum of women experiencing primary infertility and those experiencing secondary infertility, then analyse the relationship between these hormones.

Materials and Methods

The study was carried out in Al-Ramadi Teaching Hospital for Women and Children in Anbar, Iraq, from August 23, 2023, to December 31, 2023.

This study comprised a total of 90 samples, consisting of 60 women diagnosed with infertility (30 with main infertility and 30 with secondary infertility). Additionally, 30 healthy women were included as a control group.All those aged 18 to 45 years old. The healthy women's group was selected based on their regular menstrual cycle, which ranged from 26 to 30 days. These women had no prior history of endocrine issues and did not use oral contraceptives or any medications for chronic conditions such as hypertension or diabetes.The hormonal analysis was conducted using the MAGLUMI® X3 Snibe diagnostic system from Germany, which utilises the Fully-auto Chemiluminescence Immunoassay (CLIA) method. IBM The Statistical Package for the Social Sciences (IBM SPSS – version 28) and Gen Stat software were utilised to identify the impact of treatments on the study parameters.

Results

The study comprised 90 samples of women aged 18-45, separated into three groups, with each group consisting of 30 samples. The first group consisted of women with primary infertility (T1), the second group consisted of women with secondary infertility (T2), and the last group consisted of fertile women (Tc) serving as the control group. This investigation excluded any other diseases that affected the variations.

Table 1: Comparative Results of Serum Hormones in Both Groups.

	FSH	LH	TSH	T3	T4	E2	PRL
Primary Infertile Females (T1)	5.51[a]± 0.18	10.39[a]± 0.45	1.74[a]± 0.20	1.34[a]±0.06	8.16[a]± 0.18	42.1[a]± 0.93	24.0[a]± 0.97
Secondary Infertile Females (T2)	5.34[a]± 0.29	12.39[a]± 0.63	1.69[a]±0.13	1.17[a]± 0.07	8.14[a]± 0.24	48.1[a]± 0.98	22.7[a]± 0.94
Fertile Females (Tc)	2.55[b]± 0.21	3.40[b]± 0.32	1.47[a]± 0.16	0.92[b]± 0.16	5.86[b]± 0.39	71.0[b]± 1.25	5.8[b]± 0.40

Means having with different letters in same column differed significantly. ** (P≤0.01).

The study showed that serum FSH levels were significantly higher (p≤0.01) inT_1patients (5.51 ± 0.18mlu/ml) and T2 patients (5.34 ± 0.29 mlu/ml) compared to (Tc) control group (2.55 ± 0.21 mlu/ml), No significantly different between T1andT2 .as shown in figure (1).

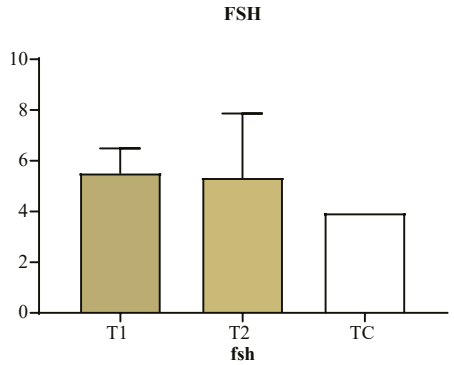

Figure 1: Means ± SE of FSH in the Serum of Primary and Secondary Patients and Control.

The results of this study showed that LH was increased significantly (p≤0.01) in patient with primary and secondary infertility (10.39 ∓ mlu/ml, 12.39 ∓ 0.63 mlu/ml) respectively compared to healthy women in control group 3.40 ∓ 0.32 mlu/ml and no significantly different between primary and secondary infertile groups as shown in figure (2)

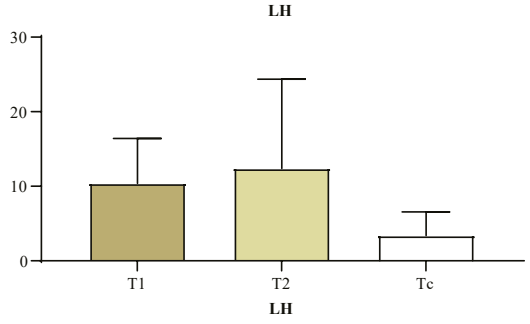

Figure 2: Means ± SE of LH in the Serum of Primary and Secondary Patients and Control.

The results of this study found that no statistically significant difference in serum TSH level between T_1, T_2 and T_c. primary infertility patient 1.74 ∓ 0.20 ulU/ml, secondary infertility patient 1.69 ∓ 0.13ulU/ml and healthy women1.47 ∓ 0.16ulU/ml. as shown in figure (3).

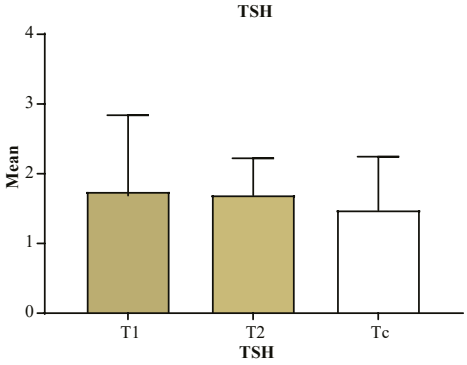

Figure 3: Means ± SE of TSH in the Serum of Primary and Secondary Patients and Control.

The study showed that serumT3 levels were significantly higher (p≤0.01) in primary and secondary infertility patient group (1.34 ± 0.06ng/ml, 1.171 ± 0.07ng/ml) respectively than healthy women (control group) 0.92 ± 0.16ng/ml, and no significant differences between T_1andT_2 groups as shown in figure (4).

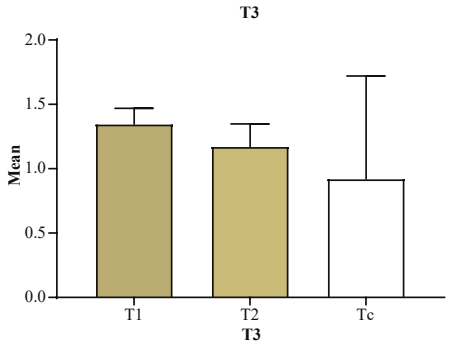

Figure 4: Mean ± SE of T3in the Serum of Primary and Secondary Patients and Control.

In recent study the mean serum concentration of T4was significantly higher (p≤0.01) in primary and secondary infertility patient group (8.16 ± 0.18mg/dl, 0.14 ± 0.24 mg/dl) respectively than healthy women (control group)5.86

± 0.39 mg/dl, and no significant differences between T_1andT_2 groups as shown in figure (5).

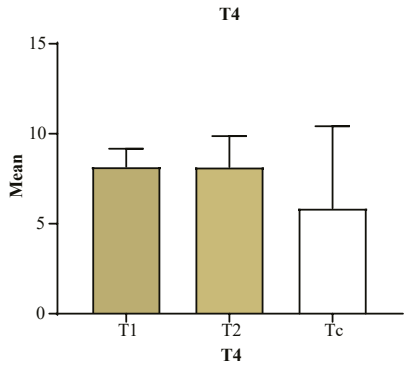

Figure 5: Means ± SE of Thyroxin (T4) in the Serum of Primary and Secondary Patients and Control.

Our results showed a decrease in E2in infertile women, there was a significant reduction in the level of the estradiol hormone (E2) among infertile women in both types primary and secondary compared to the healthy group (42.1 ± 0.93, 48.1 ± 0.98,71.0 ± 1.25pg/ml respectively) with a probability level (P ≤0.01) as demonstrated in Figure (6).

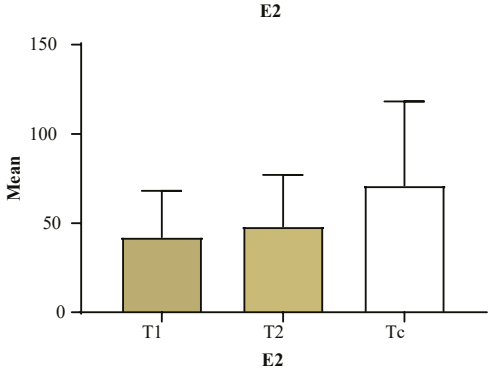

Figure 6: Means ± SE of Estradiol Hormone (E2) in the Serum of Primary and Secondary Patients and Control.

The current study showed that there is a statistically significant increase in serum prolactin levels of both type 1 and type 2 infertility group (24.0 ± 0.97, 22.7 ± 0.94ng/ml) relative to control group 5.8 ± 0.40 ng/ml and no significant differences between T_1andT_2 groups as shown in figure (7).

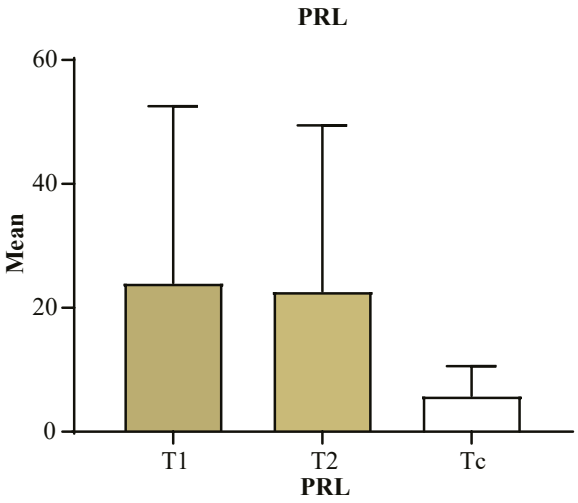

Figure 7: Means ± SE of Prolactin in the Serum of Primary and Secondary Patients and Control.

Correlation among Hormones

The study showed significant positive correlation between FSH with LH (r: 0.560**), T3 (0.303**), T4 (r: 0.235*) and Prolactin (0.220*), and negative correlation between FSH and E_2 (r:-0.327**),The study revealed a significant positive correlation between LH with T3(r: 0.282**), T4(r: 0.270**) .Also the research finds a negative correlation between TSH andE2(r:-0.267*). In recent study T3 shown appositive correlation with T4(r: 0.934**), and negative correlation with E2 (r:-0.642**),T4 shown a significant negative correlation with E2(r:-0.519**) as shown in table 2.

Table2: Correlation of Hormones in this Study.

	FSH	LH	TSH	T3	T4	E2	PRL
FSH Pearson correlation	1	.560**	-.069	.303**	.327**	.235*	.220*
LH Pearson correlation	.560**	1	-.189	.282**	.270**	.101	-.112
TSH Pearson correlation	-.069	-.189	1	.054	-.014	-.267*	.060
T3 Pearson correlation	.303**	.282**	.054	1	.934**	-.642**	.109
T4 Pearson correlation	.235*	.270**	-.014	.934**	1	-.519**	.188
E2 Pearson correlation	-.327**	.101	-.267*	-.642**	-.519	1	-.291**
PRL Pearson correlation	.220*	-.112	.060	.109	.188	-.291	1

**Correlation is significant at the 0.01level (2-tailed)
* Correlation is significant at the 0.05 level (2-tailed)

Discussion

The elevated levels of follicle-stimulating hormone (FSH) observed in these patients suggest possible ovarian malfunction. FSH plays a crucial role in regulating the maturation and growth of eggs, making it a key hormone in this process,[5] Any fluctuation in its concentration disrupts the ovulation process and disrupts the feedback mechanism, potentially indicating infertility. A significant increase in FSH concentration is a strong indication of decreased levels of oestrogen and progesterone, as well

as the absence of a feedback mechanism.[17]

Concurrence with our findings The FSH level was higher in the main infertility group compared to the control group.[18] Concurring with this discovery[19] the study revealed that the levels of follicle-stimulating hormone (FSH) in the blood serum of both primary and secondary infertile women were markedly elevated compared to the control group. Our findings corroborated the work conducted by Bheem *et al*.[20], which demonstrated that infertile women have elevated levels of follicle-stimulating hormone (FSH) compared to fertile women.[20] Furthermore, concurrence with Khalaf *et al*.[5] the serum follicle-stimulating hormone (FSH) levels in the infertile group showed a substantial rise compared to the control group. The study conducted in Pakistan corroborates our findings, indicating that levels of follicle-stimulating hormone (FSH) were higher in patients with both primary and secondary infertility.[21] Patients who were unable to conceive had markedly elevated levels of follicle-stimulating hormone (FSH).[22]

The findings of the current study contradict the findings of Zhaira *et al*.[23]'s study, which found no significant difference in the average level of FSH between women with primary and secondary infertility and healthy women.[23]

Luteinizing hormone (LH) is a pivotal hormone involved in the process of ovulation, as it triggers the release of an egg from the ovary.[24] The disruption in the secretion of the LH hormone is caused by a malfunction in the pituitary gland or an interruption in the response of the steroid hormones secreted by the gonads.[25] The elevated LH levels observed in female patients may be attributed to decreased amounts of oestrogen and progesterone. In normal circumstances, LH is suppressed due to a negative feedback process triggered by the rise in estradiol 2 and progesterone levels.[5] Elevated oestrogen levels can result in heightened LH levels, hence inducing more frequent ovulation from the ovaries. This might lead to irregularities in the menstrual cycle and hinder fertility in women.[26]

The current study's findings align with the study conducted by Seema *et al*.[18], which observed higher levels of LH in women with primary infertility compared to the control group.[18]

The findings of this investigation were consistent with the studies conducted by Khalaf *et al*.[5] a study revealed that the levels of serum luteinizing hormone were higher in infertile females compared to fertile females. Concurring with our research[27] has demonstrated that serum LH levels were markedly elevated in both primary and secondary infertile females, beyond the normal range for this hormone. An investigation conducted in Nigeria revealed a significant increase in Serum LH levels in the primary infertile group compared to the control group, which is consistent with a recent study. However, there was a significant decrease in Serum LH levels in the secondary infertile group compared to the control group, which contradicts our findings.[28]

The rise in LH and FSH levels can be due to the fact that FSH promotes the maturation of several follicles, while LH triggers ovulation by inducing the dominant follicle to break and release its eggs into the fallopian tube for implantation.[29] Elevated levels of LH and FSH stimulate the creation of testosterone in the ovaries, disrupt oestrogen production, and lead to ovulation problems.[30]

The results of a recent study confirm the findings of Seema *et al*.[18], which showed that the blood concentration of TSH in the primary infertility group is higher than the TSH concentration in the control group.[18]

The findings of this investigation are consistent with the study conducted by Abdul-Qahar *et al*.[31], which concluded that there was no statistically significant difference in TSH serum levels between the group of patients with primary and secondary infertility and healthy women.[31]

The present study corroborates the findings of Al-Hashimy *et al*.[15], who observed no significant disparities in TSH levels between infertile women and fertile women in their research.[15] Our findings align with the results of Aati and Al-Ali[32], who observed no notable disparities in TSH levels between women experiencing infertility and the control group.[32]

Our findings contradict the findings of Bari *et al*.[8], as our investigation revealed that the average serum TSH levels in women with primary and secondary infertility were considerably greater than those in women with normal fertility.[8]

T3, the more physiologically active version, exerts a distinct level of regulation on biological activity that is specific to the thyroid system.[33]

The observation clearly indicates that changed thyroid hormone levels in subclinical hyperthyroidism lead to an increase in Serum T3 levels, which in turn affects the fertility of the female reproductive system.

Consistent with our findings, the average T3 levels were elevated in the infertile patients compared to the control group, but the values remained within the normal range.[34] Aligned with the current research[35], the study revealed a substantial rise in serum T3 levels among infertile females as compared to the control group.

Unlike the current investigation, Akande *et al*.[36] discovered a notable decrease in serum T3 levels among infertile women compared to fertile women.[36]

The function of the thyroid gland can be a contributing factor to infertility, whether it is primary or secondary. Consistent with our findings, Mirza *et al*.[37] discovered that the serum thyroxin (T4) level in infertile women was higher compared to fertile ones.[37]

The infertile women group had a substantial and statistically significant reduction in T4 levels compared to the fertile group.[38]

Anovulation is caused by a disruption in the release of eggs, which is linked to low levels of estradiol being secreted outside the glands and a limited generation of progesterone.[39] Oestrogen regulates the thickness of the uterine lining and the development of eggs during the menstrual cycle.[40] It decreases bacterial infection and lowers the pH of the vagina. It decreases oestrogen levels, which consequently impacts women's sexual drive.[25]

The findings of this investigation are consistent with the study conducted by Baig *et al.*[41], which demonstrated a significant drop in the mean levels of estradiol hormone in the serum of both infertile types compared to the control group.[41]

Contrary to the findings of the recent study conducted by Ashish *et al.*[9], which reported increased levels of oestrogen in infertile Indian women, the researchers attributed this phenomenon to the presence of endometriosis.[9]

Hyperprolactinemia, characterised by elevated levels of prolactin, can be caused by conditions affecting the pituitary and hypothalamus glands. It can also be secondary to diseases affecting other organs such the ovaries, kidneys, thyroid, and liver.[36]

The results of this investigation were consistent with the findings provided by Yilmaz *et al.*[19]. A study demonstrated that serum prolactin levels are elevated in both primary and secondary infertile women compared to their fertile counterparts. Our findings are consistent with a study conducted in Najaf Governorate, which revealed a significant increase in prolactin levels in women with infertility compared to the control group. Kadium *et al.*[42] also agreed with ALdhalimi and Aldujaili[43] and Seema *et al.*[18].

Hyperprolactinemia is the underlying cause of anovulation and an irregular menstrual cycle. This condition is associated with hypothyroidism and normal levels of LH, FSH, and oestrogen. Normal levels of PRL and FSH are not associated with hyperthyroidism. However, high levels of LH and oestrogen in women who are fertile can lead to irregular menstrual cycles in the presence of hyperthyroidism.[44]

These findings were consistent with the research conducted by Al-Khafaji and Jewad[38]. Research has demonstrated a notable positive link between follicle-stimulating hormone (FSH) and levels of triiodothyronine (T3), thyroxine (T4), and luteinizing hormone (LH) in the blood serum of women experiencing infertility. Additionally, there is a negative correlation between FSH and estradiol (E2).

Our findings confirm a positive association between the prolactin hormone, as indicated by the correlations at a significant probability level ($p < 0.05$) with FSH, LH The connection between prolactin hormone and oestrogen was negative E2, T4 and T3.[45]

A significant negative correlation between TSH with LH and FSH[42] was agreement with this study.

Conclusion

The findings of this study indicate that levels of FSH, LH, T3, T4, and prolactin were significantly higher in women with primary and secondary infertility, although levels of estradiol were significantly lower. However, levels of TSH did not show a significant difference. There is a positive link between FSH and LH, T3, T4, E2, and Prolactin. However, there is a negative correlation between E2 and Thyroid hormones as well as Prolactin. There were no significant differences in the levels of reproductive hormones and thyroid hormones between the serum of women with primary infertility and those with secondary infertility.

Limitations of this Study

This study specifically examined the impact of hormonal variables on infertility in both primary and secondary infertile women.Hence, it is advisable for future studies to investigate additional components such as immunological factors and antioxidants, and to compare them across women with primary and secondary infertility.

Ethical Approval

This study has confirmed by University of Anbar Ethical Approval Committee under number of 128 in 11/12/2023

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The authors provided financing

Conflicts of Interest

There are no conflicts of interest

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