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The Association between body mass index(BMI)with some pituitary gland hormones in infertile women with and without hypothyroidism in Basra Governorate

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***Abstract*—Obesity and being overweight are rising and becoming a global issue. Obesity has a negative impact on all body systems, including the endocrine system. The present study aimed to determine whether there is an association between BMI and pituitary gland hormones in infertile women's serum in Basra City, Iraq. The study was conducted at Ibn-Gzouan Hospital for Obstetrics and Gynecology in Basra City, southern Iraq, between October 2021 and March 2022. Thestudy included 60 infertile women (30 with hypothyroidism and 30 without hypothyroidism) aged between 18 and 45 years,with a pathological period of infertility from 2 to 15 years. The studied infertile women were divided into two groups according to the measured BMI. The first group had a BMI of less than 25 (24 women) and the second had a BMI of greater than 25 (36 women).The results showed that there are significant elevations in LH level and cortisol levels as well as in LH/FSH ratio. Cortisol showed a positive correlation with BMI (r = 0.374, p = 0.025), FSH showed a positive correlation with LH level (r = 0.428, p = 0.009) in the same direction LH showed a positive correlation win LH/FSH ratio (r = 0.668, p = 0.000). In infertile women with a BMI greater than 25, FSH showed a negative correlation with the LH/FSH ratio (r = -0.342, p = 0.041). From the above results, we can conclude that BMI is an essential parameter in any treatment of women's infertility.**

Keywords*—BMI, hypothyroidism,Infertility, FSH, LH, LH/FSH ratio

I. INTRODUCTION

Infertility is seen as a global issue that affects infertile couples' health and financial well-being and their families(Jeje et al., 2016; Zargar et al., 1997). The most common type of female infertility is secondary infertility which affects women all over the world (Jokar et al., 2018).

Weight reduction and extreme weight increase in those who have a BMI of more than 27 kg/m^2 can lead to ovarian dysfunction. Weight gain has also been demonstrated to affect the efficiency and outcome of assisted reproductive techniques (Freundl et al., 2003). Fat cells and main sex organs both produce estrogen (Nelson & Bulun, 2001). As a result, being overweight or obese causes an increase in estrogen production, which the body perceives as birth control, reducing the probability of becoming pregnant. Insufficient body fat leads to insufficient estrogen levels and, as a result, menstrual irregularities with the anovulatory cycle (Eniola et al., 2012).

An increase in blood prolactin levels might be pathological, physiological, or idiopathic (Majumdar & Mangal, 2013). The most frequent endocrine condition of the hypothalamic-pituitary axis is hyperprolactinemia. Hyperprolactinemia affects anywhere from 0.4 percent of unselected normal adult females to 9 percent to 17 percent of women with reproductive health issues (Agarwal et al., 2015; Biller et al., 1999). The most essential mechanism for controlling female reproductive endocrine function is the hypothalamic-pituitary– the ovary axis is a system that connects the hypothalamus, pituitary, and ovary. The hypothalamus secretes gonadotropin releasing hormone (GnRH), which controls pituitary follicle stimulating hormone (FSH), luteinizing hormone (LH) secretion. They are also essential for ensuring a woman's reproductive health, and able to promote follicular growth and the production of sex hormones (Stamatiades et al., 2019). The aberrant secretion of GnRH, FSH, or LH caused by dysfunction in any portion of the hypothalamus-pituitary–ovary axis results in irregular menstruation or amenorrhea, as well as the reduction in infertility in women of the reproductive age. As a result, reproductive illnesses such as congenital hypogonadotropic hypogonadism, polycystic ovary syndrome, and develop premature ovarian failure (Xie et al., 2020).

The stress hormone cortisol regulates how the body reacts to physical and mental stress. Cortisol also regulates blood pressure, the immune system, anti-inflammatory

function, and protein, carbohydrate, and fat metabolism, all of which contribute to homeostasis. Hyper cortisol leads to (Cushing's syndrome), whereas a hypo of cortisol leads (to Addison's illness) (Katsu et al., 2021).Depression, anxiety, and stress-related alterations such as a faster heart rate and higher blood cortisol levels are among identified risk factors. The hypothalamic-pituitary-adrenal axis (HPA) has a role in infertility by excreting cortisol releasing hormone (CRH), Adrenocorticotropic hormone(ACTH), and cortisol, among other hormones. Changes in cortisol excretion patterns during the day have been linked to mental stress and have been found to mediate the down-regulation of the HPG axis. This effect could be due to inhibitory mechanisms at the pituitary level, which reduce FSH and LH release by GnRH. Moreover, research has shown that the ovary's endocrine status affects cortisol's effect on thehypothalamic-pituitary-gonadal(HPG) axis at different stages of the menstrual cycle. Stress may alter cortisol-excretion patterns during the menstrual cycle, influencing their hormonal profile throughout important phases of fertilization (Damti et al., 2008).

The study aimed to determine whether there is an association between BMI and pituitary gland hormones in infertile women's serum in Basra City, Iraq.

II. SUBJECTS AND METHODS:

A. *Subjects:*

It is a case-control study that included 60 infertile women (30 with hypothyroidism and 30 without hypothyroidism) aged between 18 and 45 years, with a pathological period of infertility from 2 to 15 years. The studied infertile women were divided into groups according to the measured body mass index. The first had a BMI of less than 25 as a control group (24 women), and the second had a BMI of greater than 25 (36 women). The participants visited the infertility and IVF center in Ibn-Gzouan Hospital for Obstetrics and Gynecology in Basra, southern Iraq, between October 2021 and December 2022.

B. *Methods:*

Each participant (patients and controls) had five milliliters of human blood drawn. Blood samples were 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 PRL, cortisol, FSH, and LH by Cobas e 411 kits. Body mass index was used to determine whether individuals are underweight, overweight, or obese.

BMI = (weight in kg) / (high in meter)^2

C. *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.

D. *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 the 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.

III. RESULTS

Our study included 30 infertile women with hypothyroidism and 30 infertile women without hypothyroidism. The results of our study revealed as follows:

A.Table 1 reveals that there is a non-significant difference ($p > 0.05$) between the infertile group in terms of age and duration. The BMI measurements show a highly significant increase ($P < 0.01$) in the infertile women group with a BMI >25 compared to the infertile women group with a BMI <25. LH levels, cortisol levels, and the LH/FSH ratio were all significantly higher in the infertile group with BMI greater than 25 than in the infertile group with BMI less than 25. While there is no discernible difference in FSH levels and prolactin levels between the two groups.

Table 1:A general comparison between total infertile women with BMI >25 and with BMI < 25

Total Infertile women N=60					
Parameter	BMI < 25 (N=24)		BMI > 25 (N=36)		P. Value*
	Mean	±SD	Mean	±SD	
Age(years)	28.63	6.013	28.17	7.35	0.801
Duration(years)	4.87	2.52	6.17	3.93	0.161
BMI (Kg/m$^{2)}$	16.6	5.85	30.4	4.35	0.000
Prolactin(ng/dl)	41.7	19.4	43.1	22.3	0.796
FSH (mIU/mL)	5.75	1.24	5.40	1.81	0.405
LH (mIU/mL)	5.06	1.48	6.48	2.52	0.016
Cortisol(nmol/L)	193.4	84.38	311.8	134.7	0.000
LH_ON_FSH (mIU/mL)	.935	.391	1.25	.507	0.011

B.When thyroid hormone levels in infertile with hypothyroidism were compared to those without, it was discovered that those without had much greater triiodothyronine (T3) and thyroxine (T4) levels and significantly lower thyroid stimulating hormone(TSH), as shown in the Table 2.

TABLE 2: A COMPARISON BETWEEN INFERTILE WITH AND WITHOUT HYPOTHYROIDISM

Group	Infertile with – HT N=30		Infertile without – HT N=30		P value*
Parameter	Mean	±SD	Mean	±SD	
T3 (nmol/L)	0.776	0.241	2.365	1.197	0.0001
T4 (nmol/L)	47.30	12.27	121.9	43.63	0.0001
TSH (µIU/L)	7.173	3.767	1.450	0.963	0.0001

*HT: Hypothyroidism; SD: Stander deviation; N: the number of participants

C.Table 3 reveals there is a non-significant difference (p > 0.05) in prolactin levels, FSH levels, LH levels, and LH/FSH ratio of infertile women with hypothyroidism with a BMI greater than or less than 25. Cortisol levels show a significant increase in infertile women with hypothyroidism with a BMI greater than 25 compared to infertile women with hypothyroidism with a BMI less than 25.

TABLE 3: A COMPARISON OF HORMONE LEVELS OF INFERTILE WOMEN WITH HYPOTHYROIDISM WITH BMI < 25 AND WITH BMI > 25

Infertile with hypothyroidism N=30					
Parameter	BMI < 25 (N=14)		BMI > 25 (N=16)		P. Value*
	Mean	±SD	Mean	±SD	
Prolactin(ng/dl)	40.2	20.3	39.1	22.5	0.893
FSH (mIU/mL)	6.31	1.43	5.20	1.92	0.087
LH (mIU/mL)	4.72	1.37	5.32	2.68	0.461
Cortisol(nmol/L)	184.3	78.05	284.6	119.7	0.012
LH_ON_FSH (mIU/mL)	.775	.297	1.05	.464	0.067

E. Table 4 reveals that there is a non-significant difference (p > 0.05) in prolactin levels and FSH levels in infertile women without hypothyroidism with a BMI greater than or less than 25. LH levels, cortisol levels, and LH/FSH ratio show a highly significant increase in infertile women without hypothyroidism with BMI greater than 25 compared to infertile women without hypothyroidism with BMI less than 25.

TABLE 4: A COMPARISON OF HORMONE LEVELS OF INFERTILE WOMEN WITHOUT HYPOTHYROIDISM WITH BMI < 25 AND WITH BMI >25

Infertile without hypothyroidism					
Parameter	BMI < 25 (N=10)		BMI >25 (N=20)		P. Value*
	Mean	±SD	Mean	±SD	
Prolactin(ng/dl)	43.6	19.0	46.3	22.2	0.744
FSH (mIU/mL)	5.59	1.49	5.39	1.67	0.748
LH (mIU/mL)	5.27	1.94	7.37	1.95	0.010
Cortisol(nmol/L)	208.7	91.85	333.5	144.9	0.020
LH_ON_FSH (mIU/mL)	1.03	.526	1.45	.470	0.038

E.The correlation between the study parameters (BMI, PRL, FSH, LH, Cortisol, and LH/FSH) in total infertile women with BMI >25, as in Table (5) showed that:

1. there were statistically significant positive correlations between BMI measurement and cortisol level, FSH and LH levels and LH level, and LH/FSH measurement.
2. there were statistically significant negative correlations between FSH level and LH/FSH ratio.

Table 5: Pearson Correlation between BMI and pituitary hormones in total infertile women with BMI >25

Category	Items		BMI	Prolactin	FSH	LH	Cortisol	LH_ON_FSH
BMI >25 N=36	BMI	R		.133	.185	.011	.374*	-.100-
		Sig		.439	.281	.950	.025	.563
	Prolactin	R			.202	.236	.053	.017
		Sig			.238	.166	.760	.921
		N				36	36	36
	FSH	R				.428**	-.217-	-.342-*
		Sig				.009	.203	.041
	LH	R					.163	.668**
		Sig					.342	.000
	Cortisol	R						.287
		Sig						.090
	LH_ON_FSH	R						
		Sig						

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

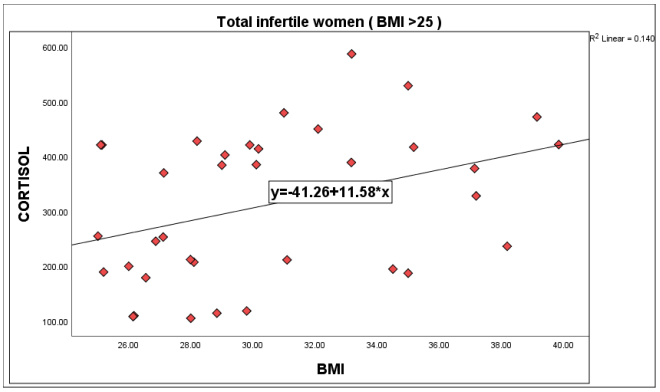

Figure 1: Regression curve of the correlation between BMI and cortisol level in total infertile women with BMI >25

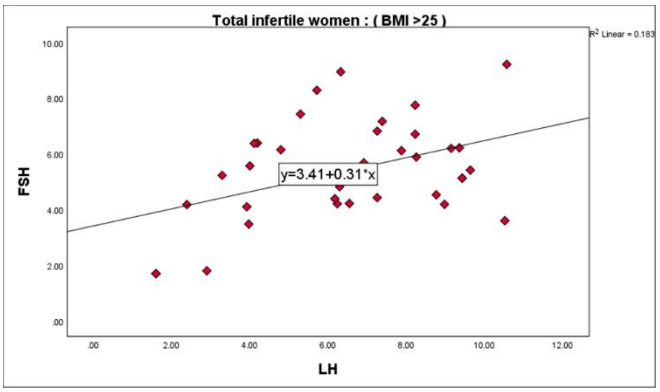

Figure 2: Regression curve of the correlation between FSH and LH levels in total infertile women with BMI >25

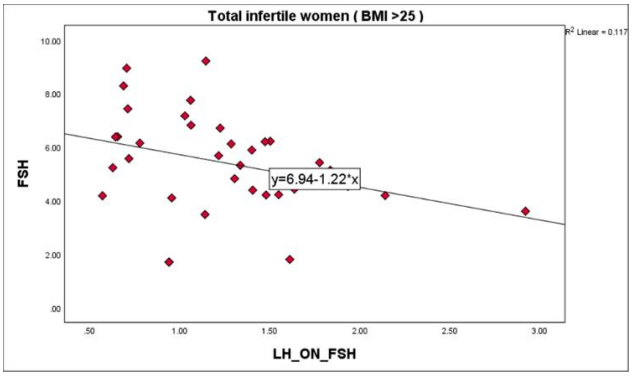

Figure 3: Regression curve of the correlation between FSH and LH-to-FSH ratio in total infertile women with BMI >25

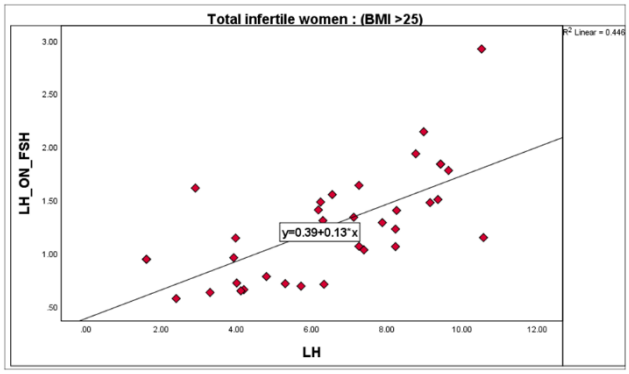

Figure 4: Regression curve of the correlation between LH and LH-to-FSH ratio in total infertile women with BMI >25

IV. DISCUSSION

Table 1 indicates a highly significant increase in BMI measurement (P <0.01) in total infertile women with and without hypothyroidism. Our study's findings agree with what was reported by Sampath (2007); they discovered that 31.5 percent of 1702 referred infertile women showed dysfunction in the thyroid gland in the form of overt or subclinical hypothyroidism. When clinical hypothyroidism symptoms were examined, a weight increase was seen in 62.5 percent of infertile women with subclinical hypothyroidism and 53.8 percent of those with overt hypothyroidism (Sampath et al., 2007).

Hypothyroidism is associated with decreased thermogenesis and metabolic activity, a greater BMI, and an increased incidence of obesity. Research data suggests that even mild thyroid malfunction in subclinical hypothyroidism is associated with considerable weight alterations and serves as a risk factor for obesity (Sanyal & Raychaudhuri, 2016).

Clinical and biochemical hallmarks of poly cystic ovarian syndrome (PCOS) comprise reproductive disruption and hyperandrogenism traits. Based on epidemiological and genetic research, PCOS is also highly connected with obesity. Consequently, PCOS often emerges in women genetically predisposed to its development and who have acquired weight (Barber et al., 2015).

Our results agree with what was reported by Neubronner (2021), who found among 389 infertile women, 134 were identified as having PCOS, whereas the remaining 255 were comprised infertile women without PCOS. Generally, 45.2 percent of women had a body mass index of more than 23 kg/m2. Compared to infertile women without PCOS, women with PCOS had a higher body mass index (mean standard deviation): 25.14 ±6.46 vs 23.08± 4.08, p < 0.001(Neubronner et al., 2021).

Table 2 shows that the levels of T3 and T4 in the blood of infertile women with hypothyroidism were much lower than those of infertile women without hypothyroidism, while the same table reveals a highly significant increase ($p < 0.01$) in the level of TSH in infertile women with hypothyroidism compared to infertile women without hypothyroidism.Investigations by Al-Deresawi (2017) demonstrated that serum TSH levels were considerably higher among an infertile group with hypothyroidism ($p< 0.01$) than those without hypothyroidism. The infertile women with hypothyroidism had lower T3 and T4 levels than those without hypothyroidism ($p< 0.05$). This variation in the mean value of the thyroid gland fails to produce a sufficient amount of T3 and T4; on the other hand, there was an increase in levels of TSH, which means the patients are suffering from hypothyroidism. Hypothyroidism can be caused by many things, like an injury to the thyroid or exposure to radiation (Al-Deresawi *et al.*, 2017). Hypothyroidism may arise when the hypothalamus or pituitary gland does not stimulate the thyroid gland enough. This can happen if the main gland fails to function correctly. In the United States, hypothyroidism is most often brought on by autoimmune disorders that affect the thyroid (Gaitonde *et al.*, 2012).

Table 3 shows that there is no significant difference in prolactin levels between infertile women with hypothyroidism who have a BMI of less than or greater than 25. Hypothyroidism was found in 24-28 percent of women with primary and secondary infertility, according to Bari (2020). In hypothyroidism, increasedthyroid releasing hormone(TRH) synthesis increases both TSH and prolactin production, resulting in hyperprolactinemia and altered gonadotropin-releasing hormone secretion. As a consequence, the reaction of luteinizing hormone is delayed (LH), which in turn leads to abnormal follicular growth and ovulation. Additionally, an inadequate corpus luteum contributes to the problem (Bari et al., 2020).

By comparing FSH and LH levels among infertile women with hypothyroidism with BMI less than or more than 25, it was found that there was a non-significant statistical difference in levels of FSH and LH Table 3. According to Singh (2016), all 15 patients had signs of hypothyroidism and menstrual abnormalities. Women with hypothyroidism have elevated prolactin and luteinizing hormone levels but normal levels of stimulating follicle hormone (Dr Asim

Singh, 2016). In hypothyroidism, an increase in thyrotropin-releasing hormone (TRH) synthesis promotes both thyrotropin-stimulating hormone (TSH) and prolactin secretion, which ultimately results in hyperprolactinemia and altered the secretion of gonadotropin-releasing hormone (GnRH) (Parijatham & Saikumar, 2014).In women, the gonadotropin production of LH may be stimulated by TRH, but not the secretion of FSH, during both the early follicular and the mid-luteal stages of the menstrual cycle (Colon et al., 1988).

As shown in Table 3, cortisol hormone levels showed a highly significant increase in the infertile women with hypothyroidism with BMI more than 25 compared to less than 25. According to Siriwardhane (2019), 10,626 women with hypothyroidism exhibited elevated cortisol levels. Cortisol is a steroid hormone produced by the adrenal gland and distributed throughout the body in response to stress(Siriwardhane et al., 2019). According to Iranmanesh (1990), higher cortisol levels in hypothyroidism in women might be attributed to impaired cortisol metabolic clearance and a reduction in cortisol negative feedback on the hypothalamic-pituitary-adrenal axis (Iranmanesh et al., 1990).

The ratio of LH/FSH in Table 3 shows that there is no significant difference in infertile women with hypothyroidism who have a BMI of less than or greater than 25. According to Sarma (2015) research on hypothyroid women, elevated levels of prolactin and LH and normal levels of FSH were found. LH:FSH ratio increased from one to six. The research also suggests that the changed hormonal state of gonadotropins may be responsible for the irregular menstrual cycle and predispose hypothyroid women to the polycystic ovarian syndrome. Menstrual abnormalities and altered gonadotropin rhythms are reported in hypothyroidism and hyperthyroidism, showing that thyroid hormones play an essential role in reproductive physiology (Sarma, 2015).

Table 4illustrates that there is no significant difference in prolactin and FSH levels infertile women without hypothyroidism who have a BMI of less than or greater than 25. A study by Torre and Falorni (2007) found that hyper-PRL might cause ovulation problems and reduce fertility. Furthermore, high prolactin secretion reduces pulsatile GnRH release and impairs normal gonadal steroid synthesis. As a direct result of this, positive feedback effects at the levels of the pituitary and hypothalamus arise, which ultimately result in infertility. They also found that the high prevalence of idiopathic hyper prolactin may be attributed to not re-examining the PRL level, examining after a cycle, or the use of drugs that conflict with dopamine, a PRL secretion inhibitor, even after the drugs have been removed for some time. Another option is the patient's ingestion of medications that were not on the list known to induce high prolactin levels in the patient's medical history (La Torre & Falorni, 2007).

FSH levels in table (4) show no significant difference in FSH levels between infertile women without hypothyroidism groups. We think the limited number of participants in the research might be responsible for these results.

As demonstrated in Table 4, LH hormone levels showed a highly significant increase in the infertile women without hypothyroidism with BMI more than 25 compared to less than 25. According to research by Naderpoor (2015), the reproductive characteristics of PCOS comprised elevated androgen production and disrupted gonadotropin secretion, which results in menstrual irregularities, hirsutism, and infertility. It exhibits significant abnormalities in insulin action and beta-cell function, which provide a significantly elevated risk for glucose intolerance and Type 2 diabetes. Obesity is common in women with PCOS; 40 to 80 percent of these women are overweight or obese. PCOS clustering in families suggests a genetic vulnerability to this condition (Naderpoor et al., 2015).Laven (2002) observed increased LH concentrations in 60percent of infertile women with PCOS. It was discovered that infertile women with PCOS may have higher pulsatile LH secretion. Elevated blood LH levels may cause theca-cell compartment in the ovary to secrete androgens for an extended period of time (Laven et al., 2002).

For cortisol hormone and as shown in the Table 4, hormone levels showed a highly significant increase in the infertile women without hypothyroidism with BMI more than 25 compared to less than 25. Our results are consistent with the findings of Bjorntop and Rosmond (2000), who believe that obesity may be caused by a disruption in the hypothalamic-pituitary-adrenal axis (Björntorp & Rosmond, 2000).A case-control study by Stimson (2009), discovered that the hyperactivity of the HPA axis is the primary cause of obesity and the aetiology of the elevation of cortisol in an obese woman is that subcutaneous adipose tissue secretes cortisol by 11 beta-hydroxysteroid dehydrogenase type 1 (11 beta-HDS1), which regenerates cortisol from cortisone and contributes to whole-body cortisol regeneration (Stimson et al., 2009). The stress associated with infertility may also be reflected in the higher levels of cortisol seen in the infertile group throughout the whole menstrual cycle. These hormones are believed to be sensitive to stress and may serve as psychological stress mediators (Csemiczky et al., 2000)

A significantly substantial positive relationship ($r = 0.374$, $p = 0.025$) exists among BMI measurement and cortisol level. A simple linear regression curve of the correlation between BMI measurement and cortisol level in the infertile without hypothyroidism group is shown in Figure 1.

Sirait, (2022) discovered that stress, or more specifically, stress-associated variables, was positively related to body mass changes in PCOS people when compared to the control group (Sirait et al., 2022).

FSH and LH levels had a very substantial positive relationship ($r= 0.428$, $p=0.009$). The figure shows a simple linear regression curve for the link between FSH level and LH levels (2).

Luteinizing hormone (LH) in synergy with follicle-stimulating hormone (FSH) stimulates normal follicular growth and ovulation. Optimal follicle development with subsequent ovulation requires the complex interaction of

FSH, LH, and their complementary activities(Raju et al., 2013).

The FSH level and the LH/FSH ratio exhibit a negative relationship (r = - 0.342, p = 0.041). The figure shows a simple linear regression curve for the link between FSH level and LH/FSH ratio (3).

The LH-to-FSH ratio exhibited an adverse correlation with FSH (r=-0.571, P0.01). A rise in LH concentration, a greater LH/FSH ratio, and a reduction in FSH all point to a disruption in the normal gonadotropin ovarian axis (Kumar et al., 2016).

LH level and LH/FSH ratio had a very substantial positive relationship (r= 0.668, p=0.000).The figure shows a simple linear regression curve for the link between FSH level and LH levels (Figure 4).A rise in LH concentration, a higher LH/FSH ratio, showing that this ratio was changed in response to an increase in LH levels, and a drop in FSH all point to a disturbance in the normal ovarian gonadotropin axis (Kumar et al., 2016).

V. CONCLUSION

From the results of this study, we concluded that:

1- The BMI is an essential parameterin any treatment of women's infertility.

2- Serum LH and cortisol levels, as well as LH/FSH ratio, significantly increased in infertile women with BMI greater than 25 compared to the infertile women with BMI less than 25 groups.

3-There was a positive correlation between BMI and cortisol level, FSH and LH levels, and between LH level and LH/FSH ratio in total infertile women with a BMI greater than 25.

4- There was a negative correlation between FSH level and LH/FSH ratio in total infertile women with a BMI greater than 25.

VI. CONFLICTS OF INTEREST

Authors declare that they have no conflict of interest.

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