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Research Article

Role of Gonadotropin-Releasing Hormone, Leptin Hormone, Luteinizing Hormone, Follicle-Stimulating Hormone, and Obesity in Polycystic Ovarian Syndrome

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Abstract— Polycystic ovarian syndrome (PCOS) is an endocrine disorder that affects women and impacts the ovaries. Obesity, genetics, and the environment are major causes of PCOS. Many disorders are associated with PCOS such as anovulation, hyperinsulinemia, and trouble with the hypothalamus-pituitary-ovary axis. Luteinizing hormone (LH), follicle stimulating hormone (FSH), and gonadotropin-releasing hormone (GnRH) are some of the hormones affected in PCOS. A high leptin level in obese women is the main cause for elevation of GnRH. The aim of this study is to determine the roles of GnRH, leptin, LH, and FSH in the occurrence of polycystic ovarian syndrome. A biochemical study was carried out from January to march 2024, involving 100 samples from Iraqi women suffered from PCOS collected from Al-Zahraa teaching hospital and Al-Diwaniyah hospital of children ,alongside 100 samples from healthy women. Measurement of GnRH , Leptin ,LH , FSH concentration were achieved by using the enzyme-linked immunosorbent assay (ELISA) kit. The P-value test was utilized to analyze the data and determine the statistical significance of the study results. The concentrations of GnRH, leptin, LH, and FSH hormones were elevated in PCOS patients compared to the control group. Significant differences ($P < 0.05$) were observed in these parameters between PCOS patients and the control group, with a P-value of 0.0001* for all parameters. Elevated levels of GnRH, leptin, LH, and FSH are highly associated with the occurrence of polycystic ovarian syndrome (PCOS) and contribute to hormonal imbalances depending on the stage of the condition. There is a correlation between leptin and GnRH: elevated leptin levels in obese women lead to increased stimulation of GnRH from the hypothalamus, which, in turn, stimulates the pituitary gland to produce more LH and FSH. Obesity is considered a primary factor in the elevation of GnRH levels in PCOS, resulting in symptoms such as hyperandrogenism and hyperinsulinemia.

Keywords— Gonadotropin Releasing Hormone, Leptin hormone, Luteinizing Hormone, Follicle Stimulating Hormone, Polycystic Ovary Syndrome, Obesity.

1. Introduction

Polycystic ovarian syndrome is an endocrine disorder that has become a common condition in the reproductive age group. It is associated with an increase in obesity worldwide. Obesity affects 38-88% of women with PCOS. There are four types of PCOS: insulin-resistant, adrenal, inflammatory, and post-pill [1]. The incidence rate of PCOS is 21-22% among randomly selected women. The main feature of PCOS is hyperandrogenism, and there are some characteristics of PCOS disorder such as anovulation or dysfunction of ovulation and the presence of polycystic ovarian morphology. The metabolic dysfunction in most cases of PCOS is characterized by insulin resistance and compensatory hyperinsulinemia [2]. Gonadotropin-releasing hormone (GnRH) is one of the hypothalamic hormones, comprised of ten amino acids. GnRH is a portion and major regulator of the hypothalamic-pituitary-gonadal axis. Its synthesis and secretion occur in GnRH neurons in humans and it has a major role in reproduction in all vertebrates, including humans, monkeys, and pigs [3]. Human GnRH acts on its receptor located in the membrane of the pituitary gland and stimulates the secretion of luteinizing hormone and follicle-stimulating hormone. These two hormones, in turn, act on the ovary [4].

The gene of the GnRH precursor is located on chromosome eight. The pre-hormone consists of 89 amino acids, and the end product is secreted at the median eminence into the hypophysial portal bloodstream [5]. In order to stimulate the pituitary gland to produce luteinizing hormone and follicle-stimulating hormone, the pituitary gland responds to fast GnRH pulses and slow GnRH pulses, respectively [6,7].

An increase in GnRH is a hallmark of polycystic ovary syndrome (PCOS), and in women with the condition, the frequency of these pulses rises by roughly 40%. Afterwards, the ovary is stimulated to overproduce androgens due to the rise in GnRH, which causes an increase in LH production from the adenohypophysis [8]. Research in animal models suggests that polycystic ovary syndrome (PCOS) can develop when estrogens trigger brain activity instead of ovarian activity. The lack of androgen and progesterone receptors on GnRH neurons suggests that sex steroids probably exert their effects via presynaptic pathways [9]. region of the hypothalamic-pituitary-gonad route that starts with GnRH and finishes with the production of progesterone and estrogen is luteinizing hormone, a glycoprotein produced from the anterior region of the pituitary gland. Leptin influences insulin, glucocorticoids, and hunger. It is secreted by adipose tissue. The amount of fat in the body is proportional to the leptin levels in a fed condition. Consequently, animal studies have linked obesity to increased leptin levels [11].

The hypersecretion of luteinizing hormone affects around 60% of PCOS patients. Low pregnancy rates and high loss rates may be caused, in part, by an excess of luteinizing hormone (LH), which may hinder oocyte maturation [12,13]. The luteinizing hormone is thought to be a catalyst for the ovary's steroid production. In addition to its functions in ovulation and zygote implantation in the uterus, luteinizing hormone also helps regulate the length and pattern of my menstrual cycle [14]. Gonadotropins are polypeptide hormones, and follicle stimulating hormone is one of them. The adenohypophysis is the site of its synthesis and secretion by gonadotropic cells [15].

By acting on the granulosa cells in females, FSH promotes the development of oocytes. Through the hypothalamic-pituitary-gonadal axis, FSH is released in response to estrogen, which is secreted by the ovaries.[16]. Novulation occurs in polycystic ovary syndrome (PCOS) patients because their LH/FSH ratio is higher than in healthy women. [17]

2. Materials and Methods

2.1 samples collection

This study was conducted from January to March 2024 and included 100 women with PCOS (Polycystic Ovary Syndrome) and 100 healthy women. All samples were collected from Al-Zahraa Teaching Hospital and Al-Diwaniyah Children's Hospital.

2.2 Statistical Analysis:

Excel and the Statistical Package for the Social Sciences (SPSS version 26, Inc., Chicago, IL, USA) were used to conduct a statistical analysis. The results and outcomes of the current study were analyzed. Statistical significance was determined with a p-value less than 0.05 ($P < 0.05$) [18].

2.3 Ethical approval:

The Declaration of Helsinki provided the basis for the study's ethical guidelines. According to document number 1742 from the College of Biotechnology, a local ethics committee evaluated and approved the study protocol, subject information, and permission form.

3. Results

3.1 Biochemical results:

Gonadotropin-releasing hormone, leptin hormone, luteinizing hormone, and follicle stimulating hormone were measured in the blood serum of women suffering from PCOS and healthy women. The results showed that Gonadotropin-releasing hormone, leptin hormone, luteinizing hormone, and follicle stimulating hormone were significantly increased in PCOS patients compared to healthy women (P-value of 0.0001*) for GnRH, leptin hormone, LH and FSH. Table 1 displays these outcomes.

Healthy women had an average concentration of 185.96±9.62 ng/l of GnRH in their serum, while PCOS patients had an average value of 398.55±83.6 ng/l. In healthy women, the concentration of leptin in serum was 32.81±27.8 ng/ml, but in PCOS patients it was 59.58±35.9 ng/ml.

The concentration of LH in serum among PCOS patients was 12.11±0.86 mlμ/ml, compared with 6.01±0.85 mlμ/ml in healthy women. The concentration of FSH in serum among PCOS patients was 11.4±0.97 mlμ/ml, compared with 4.89±1.28 mlμ/ml in healthy women. The analysis of the mean values showed a statistically significant difference between PCOS patients and healthy women, This study demonstrated an increase in the mean concentration among PCOS patients compared with the control group.

Table 1: Comparison of GnRH, Leptin, LH, and FSH levels between PCOS patients and control

Groups	GnRH (ng\l)	Leptin (ng\ml)	LH (mIμ\ml)	FSH (mIU\ml)
Control	185.96±9.62A	29.71±1.93A	6.01±0.85A	4.89±1.28A
Patients	398.55±83.6B	58.94±2.12B	12.11±0.86B	11.4±0.97B
T test	17.88	81.62	40.72	34.64
P value	<0.0001*	<0.0001*	<0.0001*	<0.0001*

Different letters between any two means vertically denote to the significant difference at P<0.05.

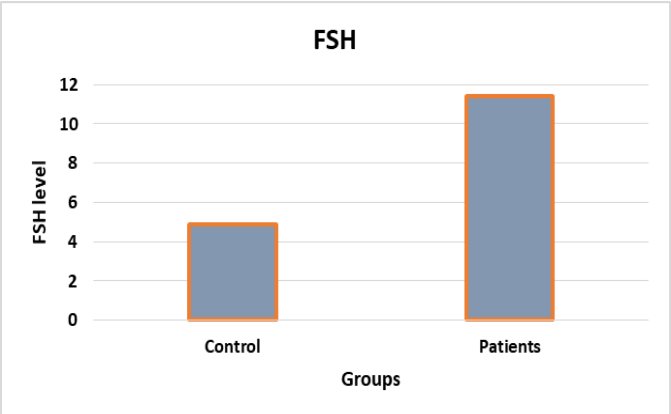

Figure 1: Comparison of FSH levels between patients and the control group

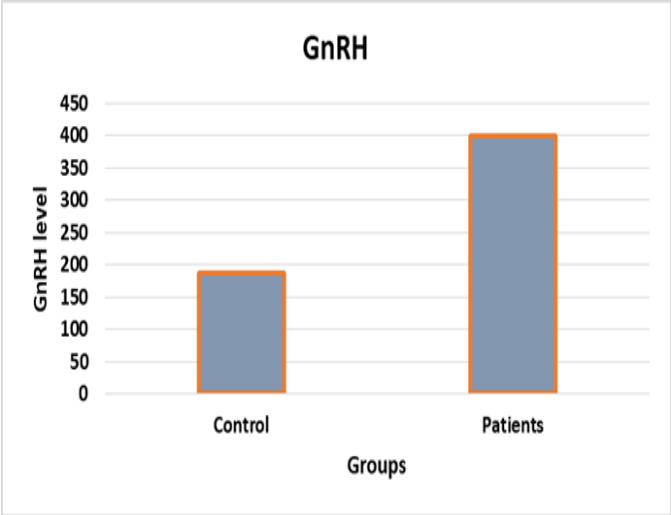

Figure 2: Comparison of GnRH levels between patients and the control group

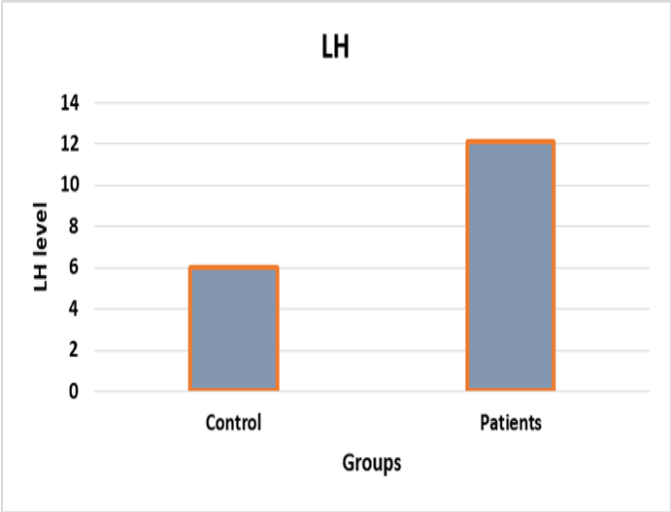

Figure 3: Comparison of LH levels between patients and the control group

The results of the correlation between GnRH concentration and the parameters measured in this study for the 100 examined PCOS patients are presented in Table 2. GnRH showed a statistically significant correlation with FSH (R = 0.208*, P < 0.01) and also exhibited a significant correlation with leptin (R = 0.733**, P < 0.01).

Table 2: Correlation among studied parameters in patients

Groups	GnRH (ng\l)	Leptin (ng\ml)	LH (mIU\ml)	FSH (mIU\ml)
Control	185.96±9.62 A	29.71±1.93 A	6.01±0.85A	4.89±1.28 A
Patients	398.55±83.6 B	58.94±2.12 B	12.11±0.86 B	11.4±0.97 B
T test	17.88	81.62	40.72	34.64
P value	<0.0001*	<0.0001*	<0.0001*	<0.0001*

***The correlation was significant at P<0.05, The correlation was significant at P<0.01**

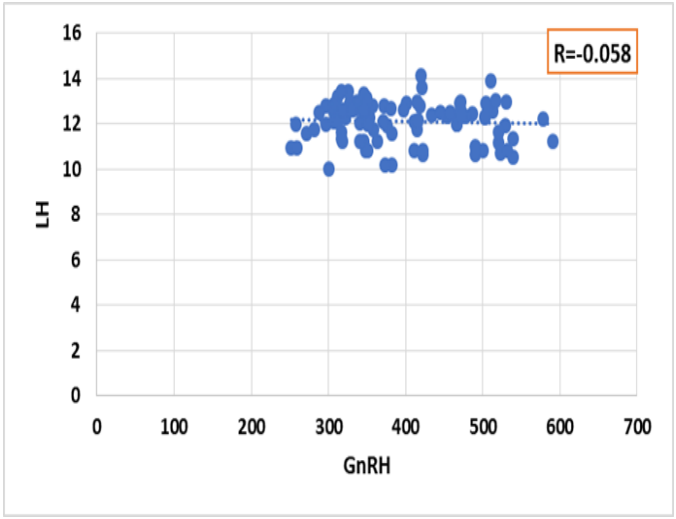

Figure 4: Correlation between GnRH levels and LH in PCOS patients

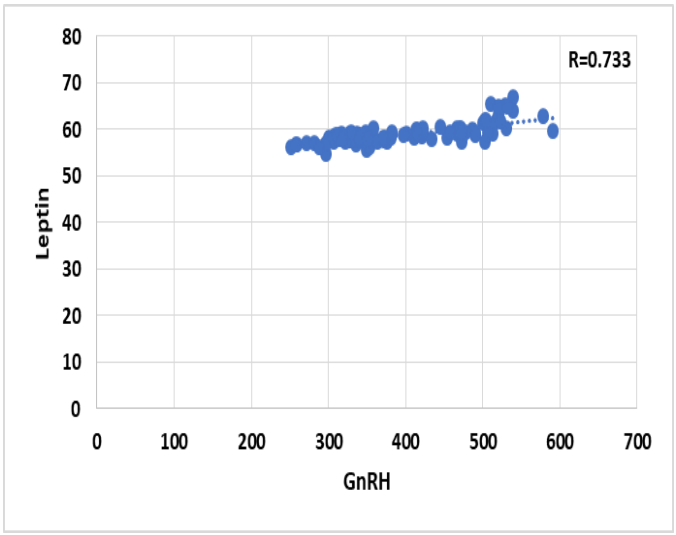

Figure 5: Correlation between GnRH levels and leptin in PCOS patients

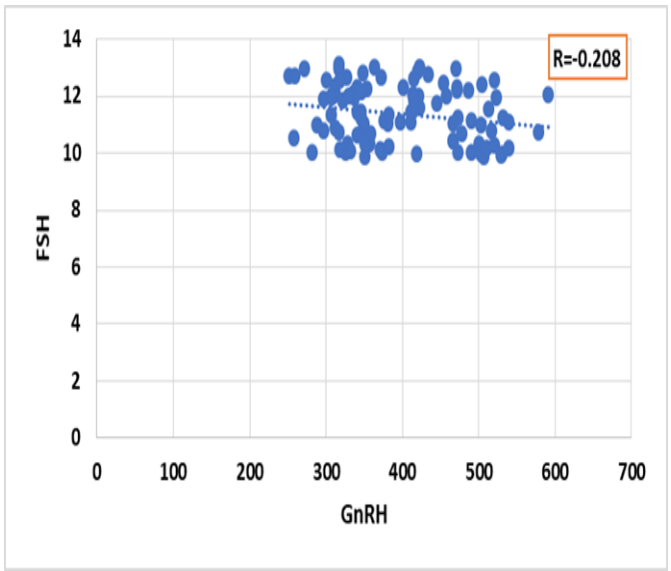

Figure 6: Correlation between GnRH levels and FSH in PCOS patients

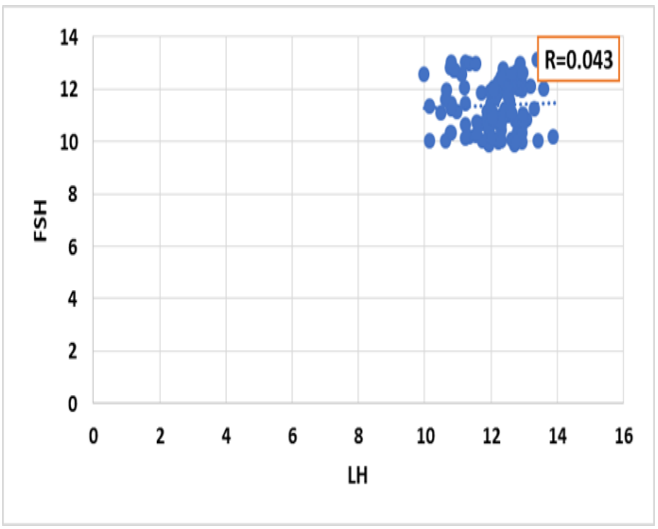

Figure 7: Correlation between FSH levels and LH in PCOS patients

4. Discussion

The results of this study demonstrated that the elevation of Patients with polycystic ovary syndrome (PCOS) have elevated serum LH and FSH levels, which are strongly associated with GnRH. This confirms what Limonta and Manea [2013] found, that when the hypothalamus secretes GnRH, it stimulates the anterior pituitary to secrete LH and FSH [19]. Zhou and his colleagues [2013] illustrated that luteinizing hormone stimulates theca cells to synthesize androstenedione from cholesterol through the action of desmolase. Granulosa cells, stimulated by FSH, subsequently convert androgens into estrogens, with aromatase transforming androstenedione into estrogen, which is then secreted by granulosa cells [20].

Homburg (1998) found that in PCOS patients, an overabundance of luteinizing hormone seems to trigger the development of early oocytes, which can lead to problems with fertilization and even miscarriage [21]. This study found that obesity is significantly associated with higher serum leptin levels in PCOS patients. These results are in line with those of Mantzoros and colleagues (1997), who demonstrated that although leptin was initially linked to obesity, it is now regarded as a molecular signal for regulating energy balance in the body, despite its original association with obesity. More recent findings point to a function for leptin in regulating the reproductive axis [22-30].

According to the results of this study, in healthy women, leptin hormone regulates the secretion and activity of gonadotropin-releasing hormone (GnRH) via acting on the hypothalamus. Because adipocytes secrete leptin, obesity raises leptin secretion. The development of hyperleptinemia and leptin resistance is a common complication of obesity. The hypothalamus is stimulated to create more GnRH by the elevated leptin levels. GnRH in turn, activates the pituitary gland to secrete of LH and FSH. This increase in LH and FSH plays a major role in the early maturation of oocytes and can contribute to anovulation in PCOS patients. When compared to a control group, Peng's [2022] research suggests that elevated leptin levels may increase the likelihood of polycystic ovary syndrome [23]. Seth (2021) demonstrated a strong correlation between polycystic ovary syndrome (PCOS) and elevated serum leptin hormone levels [24]. Elevated levels of growth hormone-releasing hormone have been found in PCOS cases [31-35]. Obesity, stress, leptin resistance, type 2 diabetes, and polycystic ovary syndrome (PCOS) are additional risk factors that might amplify the effects of the aforementioned hormonal abnormalities [18].

5. Conclusion and Future Scope

The study demonstrates that concentrations of GnRH, leptin, LH, and FSH are elevated in women with polycystic ovarian syndrome (PCOS), indicating a high correlation between these parameters and the disorder. Statistically significant differences were observed between patients with PCOS and the control group. Obesity is recognized as a primary factor contributing to the development of PCOS. Leptin, a hormone produced by adipose tissue, is elevated in obese women, and this elevation plays a central role in increasing GnRH serum levels. This hormonal interaction underscores the importance of weight loss as an effective treatment for PCOS, as it helps reduce leptin production and normalize its levels. Additionally, metformin, semaglutide, orlistat and liraglutide are employed to manage weight and improve metabolic function in women with PCOS.

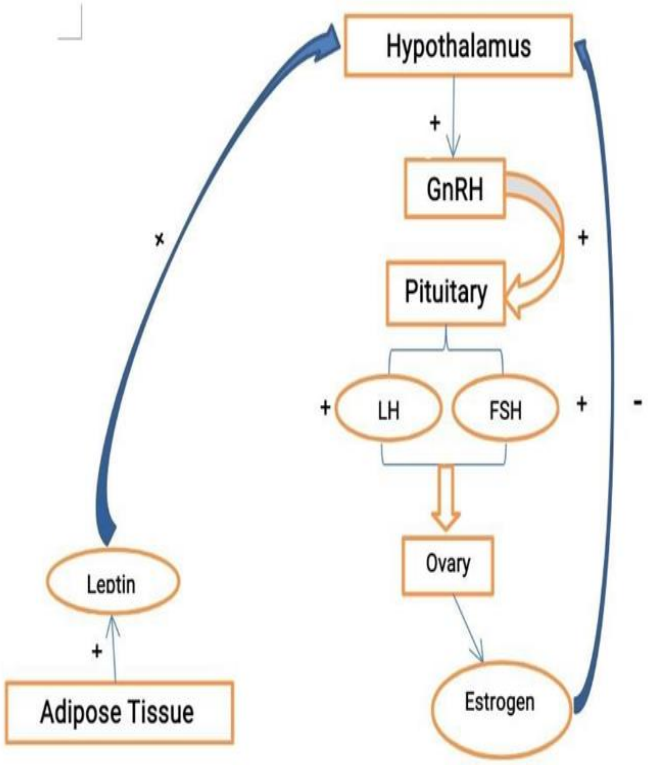

Figure 8: Illustration of the role of leptin hormone in polycystic ovarian syndrome. Adipose tissue produces a lot of leptin hormone, which in turn stimulates the hypothalamus to produce more GnRH, leading to stimulation of the anterior pituitary for secretion of LH and FSH

Conflict of interest statement
None of the authors has declared a conflict of interest with respect to this work.

Data Availability
None.

Funding Source
None.

Authors' Contributions
Thualfiqar Ghalib Turki and his team work conceived the idea and wrote the original draft of the manuscript, and the author reviewed and edited the final version.

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