

Study of the relationship between estrogen, leptin and TNF-alpha in low fertility women in Iraq

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Abstract

Infertility is one of the problems facing women and men. Estrogen (E2), leptin level disorders, and tumor necrosis factor α (TNF- α) are among the risk factors that cause infertility. The aim of the research is to study the relationship between the three criteria and their relationship to infertility or low fertility in Iraqi women in compared with fertile women (control). The current study included (120) Participating, divided into two groups. The first group (60) infertile women) who visit outpatient infertility clinics, and (60) fertile women). The study samples were collected from September 2023 to December 2024 from outpatient infertility clinics in Iraq. All participants were between the ages of (22-38) years. The Results showed that leptin and tumor necrosis factor α levels increased significantly in infertile women compared to fertile women in the luteal phase of the menstrual cycle, while estrogen levels decreased significantly. The conclusion: TNF-alpha, estrogen (E2), and leptin levels may be biomarkers for decreased fertility in women and may be helpful in identifying those who are at a high risk of low fertility.

Keywords: Infertility, Low fertility, Estrogen, Leptin, TNF-alpha

1. Introduction

The term "infertility" is frequently used to describe any heterosexual couple who, after completing all standard fertility testing, are unable to conceive a child and cannot provide a clear cause [1].

Infertility can have many different forms and causes, but for 25% of couples who visit assisted reproductive clinics, unexplained infertility is the only reason. In actuality, a number of circumstances combine to produce the appearance of infertility that cannot be explained. These factors include changes in the timing of follicle formation and ovulation, as well as decreased sperm motility and count [2]. Mammals' fertility and infertility are significantly influenced by estrogens, or steroid hormones. Although many other tissues, including the breast, also make them, the gonads and placenta are the primary producers. Both positive and negative feedback effects on the hypothalamic-pituitary axis were demonstrated. Additionally, it was shown that estrogens have an effect on target organs like the pituitary, brain, uterus, and mammary tissues [3]. It is commonly recognized that progesterone and estrogen significantly affect the endometrium and influence the expression of many genes [4].

Adipose tissues produce leptin, a byproduct of the *ob* gene, which is essential for controlling the hypothalamic-pituitary-gonadal (HPG) axis and contributing to obesity, hyperinsulinemia, and elevated insulin resistance in patients with polycystic ovarian syndrome (PCOS) [5]. Through a complicated process that links energy homeostasis and reproduction, leptin regulates the proper reproductive system physiology of females and relates with the HPG axis. However, the mechanisms underlying the interaction between leptin and the hormones of the HPG axis remain mainly indefinite, and observational studies have shown contradictory results regarding leptin change throughout a normal menstrual cycle [6]. An established concentration of leptin throughout menstrual cycle was also defined, but several studies showed inconsistent leptin behavior during the menstruation. Several reported steady additions in leptin levels from the follicular phase to reach a peak in the luteal phase [7], while others indicated a peak during the pre-ovulatory phase [8]. Nonetheless, this disparity indicates a specific function of leptin signaling throughout the menstrual cycle, while the mechanism behind this function remains to be investigated [9].

One of the factors known to contribute to the development of necrotic tumors is tumor necrosis factor alpha (TNF- α). It was later discovered to play additional crucial functions in the etiology of immunological disorders. Understanding the function mechanisms of TNF- α will therefore make it easier to use the right tools for illness management [10]. In a recent study [11], among infertile women with PCOS, it was discovered that TNF inhibitors have some beneficial uses. Infertile PCOS patients undergoing IVF-ET can then benefit from the more substantial overall therapeutic impact. TNF- α level in infertile women with endometriosis have been assessed more recently. The TNF- α value was considerably higher in individuals with severe endometriosis disorders than in other patients with infertility instances. The study recommended more research to learn more about TNF- α 's function and prognostic significance in these kinds of illnesses [12].

2. Materials and methods

2.1 Patients and Sample collection (blood)

This study was conducted on women with low fertility (infertility). The woman was diagnosed by specialist physicians. The current study samples included (120) Participating, divided into two groups. The first group (60 infertile women) who visit outpatient infertility clinics and (60 fertile women) were collected from women during the luteal phase of menstrual cycle attending out infertility clinics in Iraq through the period from September 2023 to December 2024. The current study excluded: (a) females with irregular menstrual cycles and gynecological diseases. Five milliliters of venous blood was collected from all patients and control samples and then centrifugation of samples for five rpm for 10 min to obtain serum and then transferred to clean test tubes for serological (biochemical) tests. The concentrations of circulating estrogen (E2), leptin level, and tumor

necrosis factor α (TNF- α) in serum were evaluated using viable ELISA kits, according to the manufacturer's guidelines (Cat. No: MBS2606149, MBS 727499 and MBS267654, respectively).

2.2 Statistical analysis

The SPSS software was used to statistical analysis. The *p*-value was calculated using the least significant difference approach and an independent t-test. A *p*-value ≥ 0.05 was considered to statistically significant, and all data are expressed as the Mean \pm Standard Division.

3. Results and Discussion

The results showed that significantly increased in leptin and TNF- α levels in infertile women compared to fertile women during the luteal phase of the menstrual cycle, while estrogen (E2) levels significantly decreased (table 1).

The results of the correlation in Figure (1) indicate a significantly positive correlation ($r = 0.823$) between Leptin and TNF- α concentrations in Infertile women.

Table 1: Concentrations of Estrogen, Leptin and TNF- α in Infertile and Fertile women

Groups parameters	Infertile women (Patients)	Fertile women (Control)	<i>p</i> - value
Age (years)	30.44 \pm 4.16	30.36 \pm 3.9	0.844
BMI (kg/m ²)	25.1 \pm 7.13	24.95 \pm 1.21	0.523
Estrogen (pg/ml)	93.13 \pm 14.55	207.25 \pm 5.44	0.000*
Leptin (ng/ml)	36.99 \pm 2.90	28.22 \pm 1.1	0.001*
TNF- α (ng/ml)	205.88 \pm 2.16	67.45 \pm 4.42	0.000*

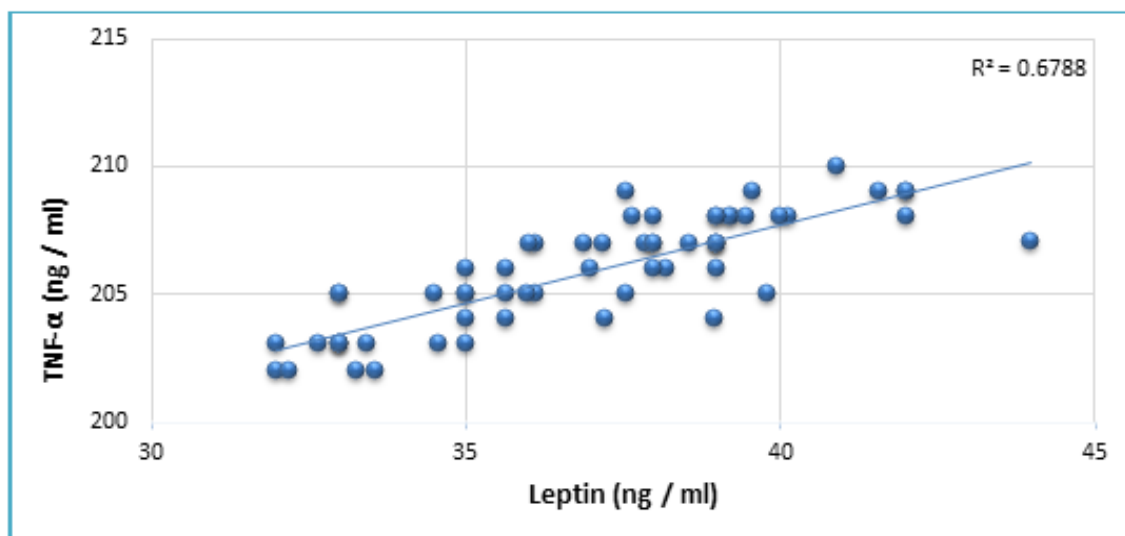


Figure (1): Correlation between Leptin (ng/ml) and TNF- α (ng/ml) concentration in infertile women.

There is still a lack of understanding regarding the evaluation and management of the reproductive system due to infertility. To determine the precise etiology of infertility and the most effective diagnostic biomarker, numerous investigations have been conducted. Nonetheless, one of the most effective biomarkers has been identified as leptin. The binding and stimulating specific receptors of leptin, which are present in numerous tissues, example the female HPO axis, leptin exhibits biological activities. By inducing the production of gonado-trophin releasing hormone, gonado-trophins, and aromatase enzymes from the brain, pituitary gland, and ovaries, respectively, leptin contributes to the activity of the HPO axis [13, 14].

Furthermore, the data showed that a high concentration of leptin inhibits the HPO axis, folliculo-genesis, physiology of ovaries, steroid-genesis, the synthesis and prostaglandin and oxytocin released, all of which have detrimental impacts on female reproduction [15].

According to the current findings, ovarian steroidogenesis, folliculogenesis, and oogenesis were all suppressed by increased leptin concentration. The findings concur with TAFVIZI that decreased in the levels of (estradiol) and ova quality are poor linked to high levels of leptin [16]. Thus, it is possible that leptin levels are linked to female infertility and that this may help to explain some of these cases. According to certain research, infertile women had greater serum leptin levels than fertile ones [17], However, other research revealed that infertile women's leptin levels did not differ significantly from those of fertile women [18].

TNF- α , The body's immune response depends on the cytokines, which are also important for controlling inflammation, which is increasingly understood to affect many facets of reproductive physiology [19].

Additionally, this investigation revealed that the concentration of TNF- α was considerably greater in infertile women than in healthy women; the findings are consistent with those of Saym *et al* [20].

According to the analysis by [21], infertile women had greater levels of inflammatory indicators than control women. In addition to this supporting data, another recent study [22] was backed by the previously mentioned studies that mentioned elevated TNF α levels in infertility conditions, suggesting the need for additional research using sophisticated techniques and carefully chosen patients to ascertain the role of TNF- α in infertility. It was discovered that when infertility was present, the levels of indicators of inflammation rose.

TNF- α level in infertile women with endometriosis have been assessed more recently. The TNF- α value was considerably higher in individuals with severe endometriosis disorders than in other patients with infertility instances. The study recommended more research to learn more about TNF- α 's function and prognostic significance in these kinds of illnesses [23].

The cause of the positive correlation between leptin and tumor necrosis factor, Adipocytes are directly stimulated to create more leptin, a lipostatic factor, by tumor necrosis factor (TNF)- α . The specific TNF receptor (TNFR) that mediates this response is still unclear [24].

4. Conclusions

This study demonstrated that the immunological profile of infertile women differed from that of fertile women, with significantly higher levels of leptin and TNF- α and lower levels of estrogen. These findings suggest that although TNF- α and leptin are important markers of infertility, they may not have a direct impact on pregnancy success.

5. References

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