RESEARCH ARTICLE

Effect of Biochemical Changes on Female Infertility, Especially "Leptin and Adiponectin" in Eastern Uttar Pradesh

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Abstract

Background: Infertility is one of women's most serious clinical problems during their reproductive lives. However, a high body mass index (BMI) and obesity are linked with unhealthy eating patterns and a sedentary lifestyle and have contributed to infertility. Obesity, on the other hand, has been linked to a high rate of infertility over the last 10 years. Additionally, low levels of sex hormones follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estrogen, progesterone, and testosterone play a significant role in causing infertility, which has a significant impact on the reproductive system. Adipokines are produced by adipose tissue, and adipocytes, including adiponectin and leptin, affect the reproductive organs. Therefore, to comprehend infertility more deeply, it is crucial to assess adipokines and sex hormones. So, the current study involved evaluating the effectiveness and level of adiponectin and leptin in infertility and fertile women of the same reproductive age, along with other hormones like insulin, insulin resistance, FSH, LH, testosterone, and prolactin.

Materials and methods: This study took 56 fertile women to act as a control in their reproductive years as controls and 100 women who have experienced infertility. Cases considerably outperformed controls regarding —BMI, waist-to-hip (W/H) ratio, insulin, and insulin resistance.

Results: Follicle-stimulating hormone (FSH), LH, prolactin, and testosterone levels in cases were higher than in controls. But though adiponectin levels were lower in patients than in controls, leptin levels were higher.

Conclusion: Given that adipokines are regulated by sex hormones, they likely contribute to infertility.

Keywords: Adiponectin, Folic acid stimulating hormone, Infertility, Leptin, Obesity, Prolactin, Testosterone.

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Introduction

Worldwide, unhealthy dietary habits lead to obesity and a higher risk of infertility. Infertility is an important additional health concern for women of reproductive age.[1] However, other clinical symptoms, as well as the loss of the ability to conceive after 1 year of sexual activity without protection, are associated with infertility.[1] Around 9–10% of the population in India suffers from infertility.[2] Obesity and metabolic disorders impact the female reproductive system. Another factor, polycystic ovarian syndrome (PCOS), which is linked to infertility and obesity,[1,2] is characterized by an anovulatory cycle and hyperandrogenemia and is associated with an irregular menstrual period, a higher risk of miscarriage, and a lower rate of conception.[2] A variety of biochemical concentration ranges, including insulin and insulin-like growth factors, have an impact on several reproductive processes, including steroidogenesis, folliculogenesis, and ovulation physiology.[1] Polycystic ovaries, hyperandrogenemia, dyslipidemia, insulin resistance, hyperinsulinemia, and obesity are among the causes of infertility that are highlighted.[3] Insulin resistance is frequently used to encourage ovulation and improve women's fertility because it is a major factor in PCOS.[2]

Follicle-stimulating hormone (FSH) also contributes to the maturation of the preovulatory follicle by triggering the activation of granulose cell aromatase and the enzymes necessary for progesterone production. Additionally, it activates the granules cell's LH receptor, which triggers the onset of ovulation and the development of the corpus luteum in response to the mid-cycle LH surge.[3,4] To maintain luteal function during the first 2 weeks of pregnancy, LH and human chorionic gonadotropin are needed. Hyperprolactinemia, which is associated with luteal phase abnormalities and ovulatory disorders, affects infertility.[4,5] Elevated testosterone has been associated with an increased rate of PCOS, a septate uterus, and FSH/LH inversion.[4]

White adipose tissue has various uses and performs the role of an endocrine organ, secreting adipokines and energy.[1] Adipokines include adiponectin, leptin, ghrelin, omentin, and chemerin.[14] Adiponectin is a beneficial adipokine because it improves insulin sensitivity, protects against atherosclerosis, and

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lowers inflammation. The hypothalamus, pituitary, ovary, oocyte, and embryonic levels are affected by leptin,[6] and it increases the insulin sensitivity of peripheral tissue.[6] A new appetite mediator called leptin that supports the gonadotropin-releasing hormone (GnRH7–10). Therefore, this study aims to evaluate the effectiveness and level of adiponectin and leptin in infertility and fertile women of the same reproductive age, along with other hormones, such as insulin, insulin resistance, FSH, LH, testosterone, and prolactin.

Materials and Methods

This study consisted of 156 women between the ages of 25 and 30. The Department of Obstetrics & Gynecology at Hind Medical Science, Sitapur, Uttar Pradesh, India, carried out this research, and a few biochemical estimations have been done at the Department of Dravyaguṇa, Faculty of Àyurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. The Institutional Medical Ethics Committee approved the study, and all patients and controls enrolled after signing their written informed consent. The study considered 100 with infertility complaints. A total of 56 healthy and normal volunteer women served as controls. Cases must include infertile women and partners with normal sperm analysis, according to World Health Organization—International Committee for Monitoring Assisted Reproductive Technologies.[11] This present study followed some exclusion and inclusion criteria, which are below.

- Received hormonal replacement therapy.
- Diabetes, galactorrhea, hyperandrogenic prolactinoma, congenital adrenal hyperplasia, Cushing syndrome, and ovarian tumors.

Inclusion Criteria

They have regular ovulation cycles, a normal menstrual history, and a 2-year-old from her previous pregnancy.

Demographics, Specimen Preparation, and Biochemical Analysis

This study included detailed patient history, as well as anthropological parameters, such as weight, height, and BMI, which were assessed. Harpenden calipers were used to measure the thickness of the skin folds. On the 3rd day of the menstrual cycle, 5–6 mL of blood samples were collected by venipuncture, and serum was separated by centrifugation and then used to analyze fasting blood sugar, triglycerides, total cholesterol, and high-density lipoprotein (HDL). For further analysis, the serum is stored at 20°C. Serum concentrations of insulin, FSH, LH, prolactin, testosterone, leptin, and adiponectin were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (ENZO Life Sciences, New York). Very-low-density lipoprotein (VLDL) is determined through equation triglyceride test F-LDL-C (mg/dL) = TC-HDLC - TG/5, the Friedewald formulation for low-density lipoprotein (LDL). Model evaluation of insulin resistance homeostasis was used to calculate the insulin resistance index by comparing fasting insulin mU/L with fasting glucose mmol/L.[7–12]

Statistical Analysis

One way to analyze the factors contributing to infertility is by using SPSS (Statistical Package for Social Sciences). SPSS 16.00 version, was used to statistical analyze the data and also to analyze the factors contributing to infertility and compare it with fertility control. SPSS analysis allows researchers to compare different variables such as age, BMI, hormonal levels, and lifestyle factors between infertile and fertile control groups. This help to identify potential risk factors for infertility and determine effective methods of managing fertility control.

Results

The current investigation has found that, while BMI and W/H ratio is higher in patients than in the controls shown in Table 1, skin-fold thickness does not differ between cases and controls. Table 2 shows that while nondiabetic medications are included in the study, patients have high fasting blood sugar (FBS) but are not significantly different from controls. Total cholesterol and triglycerides are higher in comparison with controls. Compared with controls, the HDL levels in these cases are significantly lower. Between patients and controls, there was no difference between the levels of VLDL and LDL. The FSH is frequently raised but does not change significantly, according to Table 3. The levels of LH, prolactin, and testosterone in the cases are much higher than in the controls.

In comparison to controls, cases had higher insulin and insulin resistance levels. Table 4 shows that leptin levels are higher in the cases than in the controls. Adiponectin levels are typically modest and do not significantly fluctuate.

Discussion

Various studies have shown that organisms, follicular growth, and gametogenesis are all facilitated by FSH, which is insignificant in current cases compared to controls.[10] Obese suffering from (PCOS) have lower FSH levels than nonobese PCOS, which causes anovulation and infertility.[10–13] Our research also suggests that patients with PCOS have higher levels of prolactin, LH, and testosterone. Prolactin usually suppresses the ovulatory cycle by inhibiting the secretion of FSH. However, the FSH ratio and adiponectin levels were inversely correlated in PCOS patients.[14,15]

Globally, reduced GH, insulin-like growth factor-binding proteins, and sex-hormone binding globulin (SHBG) correlate with infertility.[13–15] Lowered SHBG levels, increased testosterone production in theca cells of the ovary, and increased LH release without changing follicle-stimulating levels are all consequences of hyperinsulinemia in obese women, both of which contribute

Table 1: Endpoints for fertility (controls) and infertility based on "demographic and anthropometric data"

S. no.	*Characteristics*	*Infertility group (n = 100)*	*Fertile group (n = 56)*	*p-value*
1	Age–years	25.65 ± 4.51	26.21 ± 5.78	0.619
2	BMI kg/m^2	28.49 ± 3.55	26.65 ± 3.55	0.003*
3	W/H ratio	0.98 ± 0.04	0.87 ± 0.05	0.001*
4	Skinfold	29.89 ± 5.44	28.56 ± 4.17	0.167

*Strongly suggestive

Table 2: Fasting blood sugar (FBS) rates and liver function tests (LFT) for infertility (cases) and fertility (controls)

S. no.	*FBS and lipid parameters*	*Infertility group (n = 100)*	*Fertile group (n = 56)*	*p-value*
1	Fasting blood sugar (mg/dL)	89.32 ± 10.71	86.19 ± 9.50	0.127
2	Total cholesterols (mg/dL)	154.65 ± 63.74	136.51 ± 44.47	0.069^{+}
3	TGL (mg/dL)	135.76 ± 11.94	132.54 ± 9.82	0.040*
4	HDL (mg/dL)	26.38 ± 8.92	32.75 ± 16.43	0.020*
5	VLDL (mg/dL)	122.56 ± 5 3.64	113.76 ± 44.12	0.235
6	LDL (mg/dL)	112.67 ± 44.53	112.48 ± 43.23	0.785

$^{+}$Suggestive significance; *moderately significant

Table 3: Rates of sex hormones and insulin for infertility (cases) and fertility (controls)

S. no.	*Hormones*	*Infertility group (n = 100)*	*Fertile group (n = 56)*	*p-value*
1	FSH mIU/mL	10.52 ± 17.57	8.43 ± 9.46	0.468
2	LH mIU/mL	11.78 ± 9.55	7.02 ± 5.39	<0.001**
3	Prolactin/mL	22.96 ± 13.95	17.81 ± 12.95	0.046*
4	Testosterone/mL	1.75 ± 3.29	0.67 ± 0.40	0.069^{+}
5	Insulin µIU/mL	18.93 ± 29.47	9.82 ± 14.42	0.058*
6	Insulin resistance	3.11 ± 3.77	1.78 ± 1.81	0.022*

**Strongly suggestive; $^{+}$suggestive significance; *moderately significant

Table 4: Adipokine levels in cases of infertility and fertility (controls)

S. no.	*Level*	*Infertility group (n = 100)*	*Fertile group (n = 56)*	*p-value*
1	Leptin ng/mL	10.915.32	7.07 ± 12.71	0.091^{+}
2	Adiponectin ng/mL	11.62 ± 6.95	12.89 ± 6.58	0.315

$^{+}$suggestive significance

to PCOS.[16] The hypothalamus-pituitary-gonadic axis deteriorates, resulting in an impaired ovulatory function.[17–19]

A 16 kDa, 146 amino acid polypeptide called leptin is not glycosylated.[7,8] The "ob" gene produces this leptin hormone primarily produced in adipose tissue. It is a hormone that suppresses hunger and makes people eat less. However, obese people have higher concentrations of leptin hormone.[15–17] It also affects fertility by impacting the reproductive system and aids implantation by promoting gonadal function, embryonic development, and interactions between the embryo and the endometrium.[16] Leptin induces the production of nitric oxide from adrenergic interneurons, which in turn stimulates the release of "GnRH" from "GnRH neurons" *via* activating guanylate cyclase and cyclooxygenase.[7–10]

Leptin levels are higher in obese patients with PCOS, which is associated with central adiposity rather than PCOS.[19] In comparison to controls, our study also showed slightly increased levels of leptin in patients. The stimulated females showed higher concentrations of LH, increased ovarian and uterine weight, and stimulated ovarian and uterine histology.[20] Expression of leptin receptors in syncytiotrophoblast at the maternal interface raises the possibility that leptin affects placental function in an autocrine or paracrine manner.[7] High levels of leptin could be a sign of successful reproduction.[21] However, it has been suggested that hyperleptinemia alone, free of fat mass, may be related to hypothalamic amenorrhea in females with hypothalamic amenorrhea who also have food issues and a normal weight.[22]

Reduced responses of LH and FSH to GnRH were associated with increased obesity and hyperleptinemia.[23–26] Leptin-deficient mice, which exhibit low LH and partial improvement of conceptive organs, help to explain the importance of leptin motioning in female reproduction. The treatment triggers pubertal change, and the development of conceptive organs expands LH and reestablishes fertility.[27]

Adipocytes, muscle cells, and liver cells secrete the 30 kDa protein known as adiponectin, and during adipogenesis, it is expressed in adipocytes.[28] Adiponectin is available in three different molecular weights—low molecular weight trimeric form, medium molecular weight hexameric form, and high molecular weight multimeric form. Adiponectin's main roles include enhancing fatty acid oxidation in skeletal muscle, decreasing hepatic gluconeogenesis, and increasing glucose absorption in the liver and muscle to improve insulin sensitivity. Adiponectin thus enhances insulin sensitivity and lessens lipid buildup.[29]

These receptors have seven-transmembrane structures, but unlike G protein-coupled receptors, the C-terminal portion is extracellular, whereas the N-terminal portion is cytoplasmic. The AMP-activated kinase is the primary intracellular signaling pathway, but a number of other pathways are also involved. Reproductive tissues, such as the ovary, placenta, and endometrium, have been found to have adiponectin receptors.[30] Adiponectin causes the expression of a group of proteins involved in the ovulation process, such as prostaglandin E2, cyclooxygenase-2, and vascular endothelial growth factor. To keep the ovaries healthy, adiponectin causes ovarian gene expression and steroidogenesis. Adiponectin cases were also lower in our study than in controls. Obesity, which plays a significant role in the pathogenesis of PCOS, has lower levels.[6,26] Leptin and adiponectin appear to act autocrine/paracrine in the placenta, contributing to glucose metabolism and fetal development and playing a significant role in the maternal-fetal interface. Obese people exhibited leptin resistance and

decreased serum adiponectin levels, suggesting leptin plays a role in regulating menstrual cycles.[7,20] Women's interactions with leptin and adiponectin appear to be influenced by a lifelong increase in adiposity.[30,31]

Conclusion

We conclude that although sex hormones and insulin resistance are adversely connected with adiponectin, they are positively correlated with leptin. Infertility is caused by a complicated web of related causes. The study describes how adipokines alter reproductive hormones and their function in female infertility. Future treatments for infertility will improve with a complicated web of related causes of infertility and the estimation of adiponectin and leptin as markers of adipose tissue activity.

Authors' Roles

VR: Concept and design, performance with other authors; RD: Acquisition of data, analysis, s and interpretation of data; drafting the article; final approval of the version to be published. JS: Data analysis and interpretation of data; revising the article for important intellectual content; final approval of the version to be published.

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