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Evaluation of Role of Some Adipokines and Anti-Mullerian Hormone in Women with Polycystic Ovary Syndrome in Nineveh Governorate – Iraq

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ABSTRACT. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age and one of the most important causes of poor fertility, This syndrome is accompanied by metabolic dysfunction and poor fertility. This study aimed to evaluate the role of some adipokines (chemerin and visfatin) among the causes of the disease and anti-Müllerian hormone (AMH) as a basic indicator of this syndrome, in the serum of 100 female patients, it included single and married women who do not have children (primary infertility) and women who are married but have children (secondary infertility), their ages ranged between (15-45) years, from visits to both Al-Batoul and Al-Khansaa Teaching Hospital for Obstetrics and Gynecology in Nineveh Governorate, who was diagnosed with the syndrome by obstetricians, gynecologists and poor fertility doctors, as well as 50 healthy females (single and married women) of the same ages who were considered as a control group. The results of the study showed a significant increase in the probability level ($p \leqslant 0.01$) in the level of chemerin, visfatin, and anti-Müllerian hormone (AMH). The 26% of chemerin in the serum of the women with PCOS reached single women, 26% for single women, 40% for married women, 46% for married women with primary infertility and for married women with secondary infertility was 32% compared to control, and the rate of increase in visfatin in affected women was 22% for single women, 26% for married women, 31% for married women with primary infertility and for married women with secondary infertility 21% compared to control, while the rate of increase in anti-Müllerian hormone in affected women reached 128% for single women,108% for married women, 103% for married women with primary infertility and 163% for married women with secondary infertility compared to control. We conclude from this study that chemerin, visfatin, and AMH can be used as a biomarker for early detection of PCOS and clinical signs such as poor fertility and hyperandrogenism in women with polycystic ovary syndrome.

Keywords: polycystic ovary syndrom; adipokines; chemerin; visfatin; Anti-mullerian hormone.

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Introduction

Currently, the main cause of ovulatory infertility is polycystic ovary syndrome (PCOS), which is one of the most common endocrine disorders among women of reproductive age and one of the major causes of poor fertility (Aldulaimy & Jankeer, 2023). PCOS is defined by the presence of at least two Rotterdam criteria, which include lack of ovulation, PCOS and clinical or biological hyperandrogenism, clinical hyperandrogenism (excessive hair growth and hair loss) was present in most women with PCOS. (70–80%) of afflicted women have poor fertility; nevertheless, a definitive diagnosis may only be reached after ruling out other potential reasons (Collée et al., 2021). The majority of individuals with this syndrome have obesity and insulin resistance (IR), which suggests that the molecules and hormones secreted by adipose tissue play a major role in infection with PCOS. It has been proven that adipose tissue participates in the regulation of many physiological processes, such as the immune response, glucose and lipid metabolism, through the secretion of a variety of biologically active cytokines, which are called adipokines, including chemerin and visfatin (Farshchian et al., 2014). Adipokines are secreted in the form of molecules from sebaceous glands via endocrine pathway (de Oliveira dos Santos et al., 2021).

Adipokines have significant systemic effects on target organs including brain, liver, muscle, pancreatic beta-cells, heart and blood vessels (Blüher et al., 2012). In recent years, researchers have focused on the role of adipokines in human fertility (Vázquez et al., 2015). It has been proven that many adipokines play a role in

reproductive function, especially in the physiological function of the ovary. Moreover, many studies have proven that some of these adipokines are a relationship with human ovarian follicle function and modulation of steroidogenesis (Dupont et al., 2015). Adipokines affect metabolic and endocrine signals in women with PCOS. Many of these kinetics are known to affect the regulation of the hypothalamic-pituitary-gonadal axis or change the composition of ovarian steroids in women with this syndrome. They pointed to an imbalance in the regulation of the kinetics secreted by fat cells in these women (Schüler-Toprak, et al., 2022). Women with PCOS often suffer from obesity (almost 50% are obese), They begin to have reproductive and metabolic problems in this condition, and it affects (5-10)% of women of reproductive age and is one of the most common causes of infertility in women (Abdul-Fattah et al., 2009).

Chemerin is one of the adipokines that is secreted mainly from adipose tissue, and from a wide range of cells such as ovarian cells (granulosa cells), liver cells, brown and white fat cells, and tissues such as the placenta, lungs, skeletal muscle and kidneys (Mansoori et al., 2022). It was discovered in 2007 as a novel adipokine linked to obesity and metabolic syndrome, and shown to enhance adipocyte formation and metabolism (Bongrani et al., 2019). (Schüler-Toprak, et al., 2022) indicated that chemerin participates in the excessive autophagy found in granulosa cells in women with PCOS, as it is associated with chronic inflammation. Many studies have also indicated high levels of chemerin in the serum of women with PCOS, which indicates Chemerin is one of the causes of this syndrome.

Visfatin was initially described as an adipokine in 2005. Since visfatin is an adipokine that is associated with visceral fat rather than subcutaneous fat in humans and mice, it was first proposed that visceral fat is the primary source of this adipokine (Fukuhara et al., 2005; Bundhun et al., 2017). Visfatin is present in several fat depots, including perivascular fat, although it is more significant in adipose lymphocytes, liver, muscle, trophoblast, and fetal membranes (Kurtul & Elcik, 2017). Compared to age- and BMI-matched controls, women with PCOS had higher blood visfatin levels and increased gene expression (Seow et al., 2011). After three months of metformin therapy, the level of visfatin in women with PCOS considerably dropped, suggesting that visfatin may have pro-inflammatory and pro-immune effects (Chen et al., 2013). Studies have also indicated that visfatin is one of the causes of PCOS due to its anti-inflammatory properties (Moustafa & Al-Hakeim, 2020).

Anti-Mullerian Hormone (AMH), also known as Mullerian Inhibiting Substance (MIS), is diglycoprotein and is produced in the reproductive tissues of both sexes, and Its level in the blood is determined by sex and age. Its low level in females aids in the development of the female reproductive organs until puberty, at which point the granulosa cells in the ovaries start to produce it. As the number of eggs remaining in the ovary increases, its level in the blood increases, and then begins to decrease again as menopause approaches (Clemente et al., 2022). The level of AMH in the serum of women with PCOS is (2-4) times higher compared to healthy women, as PCOS is characterized by an increase in the number of follicles, especially small pre-antral and antral follicles, which are the ones that produce AMH in the first place, and failure to mature. follicles despite initial recruitment leading to anovulation (Bhide et al., 2015). It was initially believed that this increase in the level of AMH in the serum of women with this syndrome was due to a large number of small antral follicles and pre-antral follicles, but there is evidence to support the role played by androgens. It was found that there is a positive relationship between the level of AMH and androgens in the blood. Excess production of androgens may be due to an intrinsic defect in theca cells in women with PCOS (Dewailly et al., 2014).

This study aims to evaluate the role of some adipokines (chemerin and visfatin) and anti-Müllerian hormone (AMH) in the serum of women with PCOS. It included single and married women who do not have children (primary infertility) and married women who have children (secondary infertility) in the Nineveh Governorate to determine the extent of their effect and influence.

Material and methods

Chemical material used

In this study, ready-made analyses (kits) from different international companies to estimate some adipokines (Chemerin and Visfatin), prepared by the Chinese company BT-LAB, and Anti-Mullerian Hormone, prepared by the French company Bio-Merieux.

Location and duration of study

This study was conducted on women with PCOS at Al-Batoul and Al-Khansa Teaching Hospital for Obstetrics and Gynecology and a number of private laboratories in Nineveh Governorate for the period from

January to June (2023). The study included 100 blood samples from women with PCOS (single and married), whose ages ranged between (15-45) years, after they were diagnosed by female doctors specializing in obstetrics, gynecology, and infertility based on clinical examination and ultrasound diagnosis, in addition to biochemical tests, according to a special questionnaire form prepared for this purpose, It was classified into three groups: the first group included 25 samples from unmarried (single) women with PCOS, the second group included 35 samples from married women with PCOS and primary infertility, while the third group also included 40 samples from married women with PCOS and secondary infertility, and the study also included 50 samples of healthy women (25 married and 25 single) who do not suffer from PCOS, do not suffer from any fertility problems or chronic diseases, have regular menstrual cycles, and they have same ages.

Collection and preservation of blood sample

Five ml of venous blood was collected from women after fastaining from food for (12-14) hours. The blood sample was placed in plastic tubes devoid of any anticoagulant (Jell Tube) with clean, sterile covers. It was left at room temperature for 20 minutes until the blood coagulated, Blood was then separated using a tabletop centrifuge for 15 minutes at a speed of 3000 rpm to obtain the serum. The serum was withdrawn using a micropipette and the serum was divided into plastic Ependroff tubes, and stored in the freezer at (-20) °C. Until biochemical tests are performed.

Statistical analysis

A Complete Randomized Design (C.R.D.) was used for statistical analysis of the data, and differences between the patient and control groups were found using a t-test for variables studied at the probability level ($p \leqslant 0.01$); for variables studied at the probability level ($p \leqslant 0.01$), differences between the patient and control groups were found according to marital status and primary and secondary infertility using Duncun's Multiple Range Test; this difference was deemed significant, and the mean ± standard error (Hinton, 2014) was calculated using a ready-made statistical program (IBM SDS Statistics Version 24).

Results and discussion

The results in Table 1 showed a significant increase at the probability level ($p \leqslant 0.01$) in the level of chemerin, as the percentage of increase reached 39% in the serum of patients with PCOS compared to the control. The results in Table 2 also showed a significant increase in the level chemerin in the serum of single women with PCOS increased by 26%, while the percentage of increase in the serum of married women with PCOS was 40% compared to control, while the results in Table 3 showed a significant increase in the level of chemerin in the serum of married women with PCOS and those with primary infertility was 46%, while the rate of increase in the serum of married affected women who had secondary infertility was 32% compared to control.

The results of the current study are consistent with the findings of (Aljaff, 2014; El-Omada et al., 2018; Halawa et al., 2020) that there is a significant increase in the level of chemerin in the serum of affected women with PCOS compared to control, as the results of their study on women with PCOS. (Kabil Kucur et al., 2021) found high levels of chemerin in the serum of these women compared with control, regardless of body mass index, insulin, insulin resistance, and lipid profile.

Chemerin is one of the most recently identified adipokines and through its known effects, it may be thought to act in different pathways leading to insulin resistance and metabolic-related inflammatory events, disorders that occur in women with PCOS (Yilmaz et al., 2021) The reason is due to an increased level of chemerin for its function of chemerin on glucose and lipid metabolism (energy production), as chemerin or its receptors play an essential role in the differentiation of pre-adipose cells into fat cells by reducing the expression of fat cell genes involved in glucose and lipid metabolism, and inhibiting the expression of aromatase caused by Follicle stimulating hormone (FSH), which is the main enzyme in the metabolism of sex hormones and stimulates the conversion of androgen into estrogen in adipose tissue and ovarian granulosa cells (Mansoori et al., 2022).

It has recently been known that the formation of polycystic ovaries is closely linked to the formation of abnormal steroids. It has been found that chemerin reduces estradiol secretions and inhibits the secretion of progesterone and estradiol caused by FSH in the antral follicles and granulosa cells. Some studies have indicated that chemerin is a new negative regulator of follicular steroid induced by the hormone FSH, and it has contributed

to the causes of PCOS, as many experiments have proven that chemerin plays a role in the pathophysiology of PCOS syndrome in human or animals by directly affecting the ovary (El-Omda et al., 2018).

Table 1. Level of Chemerin, Visfatin and Anti-Mullerian Hormone in the serum of affected woman with PCOS compared to control.

Studied Groups	Control			Patients		
Hormonal Variables	Level Mean ± Standard Error	% Level	% Change	Level Mean ± Standard Error **	% Level	% Change
Chemerin (ng mL^{-1})	234.51±3.1	100	-	325.55±5.0	139	39+
Visfatin (ng mL^{-1})	16.99±2.2	100	-	21.49±4.8	126	26+
Anti-Mullerian hormone (ng mL^{-1})	2.72±0.3	100	-	5.45±2.7	200	100+

The numbers followed by the sign (**) indicate significant differences at ($p \leq 0.01$) according to (T-Test). -The sign (+) means an increase.

Table 2. Level of Chemerin, Visfatin and Anti-Mullerian Hormone in the serum of affected single and married woman with PCOS compared to control.

Studied Groups	Single Control			Single Patients			Married Control			Married Patients		
Hormonal Variables	Level # Mean ± Standard Error	% Level	% Change	Level # Mean ± Standard Error**	% Level	% Change	Level # Mean ± Standard Error**	% Level	% Change	Level # Mean ± Standard Error	% Level	% Change
Chemerin (ng mL^{-1})	231.43±2.4c	100	-	292.03±4.5ab	126	26+	236.9±3.9bc	100	-	331.93±4.9a	140	40+
Visfatin (ng mL^{-1})	14.91±1.6c	100	-	18.24±1.2b	122	22+	18.03±1.8b	100	-	22.76±2.8a	126	26+
Anti-Mullerian hormone (ng mL^{-1})	2.84±0.2b	100	-	6.50±3.3a	228	128+	2.60±0.4b	100	-	5.42±1.9a	208	108+

The numbers followed by different letters horizontally indicate a significant difference at ($p \leq 0.01$) according to Duncan,s Test. The sign (+) means an increase.

Table 3. Level of Chemerin, Visfatin and Anti-Mullerian Hormone in the serum of primary and secondary infertility woman affected with PCOS compared to control.

Studied Groups	Control			Primary infertility			secondary infertility		
Hormonal Variables	Level # Mean ± Standard Error	% Level	% Change	Level # Mean ± Standard Error**	% Level	% Change	Level # Mean ± Standard Error**	% Level	% Change
Chemerin (pg mL^{-1})	236.98±3.9b	100	-	346.21±5.3a	146	46+	312.90±3.9a	132	32+
Visfatin (ng mL^{-1})	18.03±1.8b	100	-	23.72±2,4a	131	31+	21.89±2.9a	121	21+
Anti-Mullerian hormone (IU mL^{-1})	2.60±0.4b	100	-	5.28±1.7a	203	103+	6.86±1.3a	263	163+

The numbers followed by different letters horizontally indicate a significant difference at ($p \leq 0.01$) according to Duncan,s Test. The sign (+) means an increase.

The results in Table 1 showed a significant increase at the probability level ($p \leq 0.01$) in the level of visfatin, as the percentage of increase reached 26% in the serum of women with PCOS compared to the control. The results in Table 2 also showed a significant increase in the level visfatin in the serum of single women with PCOS increased by 22%, while the percentage of increase in the serum of married women with PCOS was 26% compared to control, while the results in Table 3 showed a significant increase in the level of visfatin in the serum of women with PCOS who are married and infertile. Primary by 31%, while the increase in the serum of affected married women who had secondary infertility was 21% compared to control.

The results of this study are consistent with the findings of (Kinani, 2015; Al-Ghazali et al., 2015; Omar et al., 2018) and they indicated that the exact mechanism for increasing the level of visfatin in the serum of women with PCOS is currently unknown, and this increase may be due to either weak visfatin signaling in target tissues, and a general lack of regulation in the biosynthesis of visfatin and the compensatory response in insulin-resistant and hyperinsulinemic tissues. This supports the reasons for its increased level in patients

with type 2 diabetes, and with regard to the effect of increased visfatin level as a potential contributor to insulin resistance in women with PCOS, due to the insulin-like properties of visfatin, in addition to the possible links between visfatin and insulin resistance, they also pointed to a possible role for visfatin in the development of insulin resistance that appears in women with PCOS. Due to the physiological effect of visfatin in reducing the level of glucose in the blood, visfatin binds to the insulin receptor and its location is different from the location of insulin, which causes a decrease in glucose in the blood by stimulating the use of glucose by fat cells, inflammation of the muscles, and a decrease in glucose secretion from the liver. Its observed levels have a role in the development of polycystic ovary syndrome and are positively associated with and released by obesity (Al-Ghazali et al., 2015). Recently, it has been shown that visceral adipose tissue produces visfatin, which may regulate insulin resistance, so increased visceral adipose tissue is associated with increased visfatin production and other adipokines (Fukuhara et al., 2005). Visfatin participates in ovarian energy metabolism, especially in the biosynthesis of Nicotinamide Adenine Dinucleotide (NAD+), which affects the development and growth of follicles (AL-Ghazali et al., 2015).

It has been observed that the level of visfatin increases significantly in cases of infertility, and the most common cause of infertility in women is ovulatory disorder, indicating that there is a positive relationship between the level of visfatin and infertility in women. The level of visfatin is necessary for normal reproductive function in women, as it is linked to a weak level that increases the incidence of polycystic ovary syndrome and endometriosis, which reduces fertility in women, the positive correlation between the level of visfatin in serum, body mass index, and insulin resistance contributes significantly to reproduction and neuroendocrine-related abnormalities, a high level of visfatin increases the level of infertility in women (AL-Ghazali et al., 2015).

The results in Table 1 showed a significant increase at the probability level ($p \leqslant 0.01$) in the level of Anti-Müllerian hormone (AMH), as the percentage of increase reached 100% in the serum of women with PCOS compared to control. The results in Table 2 also showed a significant increase level of AMH in the serum of single women with PCOS increased by 128%, while the percentage of increase in the serum of women with PCOS who were married was 108% compared to control, while the results in Table 3 showed a significant increase in level of AMH in the serum of women with PCOS who were married and who were they had primary infertility at a rate of 103%, while the rate of increase in the serum of married affected women who had secondary infertility was 163% compared to the control.

The current study's findings are in line with those of (EL-Omda et al., 2018; Mut et al., 2021; Ding et al., 2021; Ali et al., 2023). Granulosa cells in growing follicles, such as primary, pre-antral, and tiny follicles, release antimigraine hormone (AMH). As the follicles grow, the level of AMH produced drops and once the follicles reach the size of the dominant follicle, they disappear. Its removal from these large follicles is a critical condition for selection of the dominant follicle and continued ovulation. AMH plays a crucial role in regulating follicle formation, and it also has an inhibitory role in ovarian growth.

The inhibitory effect of AMH on the response of follicles to FSH is mediated by AMHRII via aromatase inhibition, and for this reason AMH is the focus of attention in PCOS, where the level of AMH in serum doubles, and granulosa cell production of AMH increases significantly (Pellatt et al., 2010; Kałużna et al., 2021). Decreased expression of the aromatase enzyme leads to an increase in androgens from the granulosa cells within the ovary. Androgens stimulate the requirements of the follicle in the antral and pre-antral follicle stages of follicle development. For this reason, the size of the ovary increases. Accordingly, the interaction of AMH and many androgens affects the size of the ovary and the number of follicles. antral (Chang et al., 2013). A decrease in activity of aromatase also leads to a decrease in the formation of estrogen, and a decrease in the level of estrogen in the blood leads to an increase in the secretion of luteinizing hormone (LH) through negative feedback. They also (Matsuzaki et al., 2017) indicated that AMH directly increased the pulsation and secretion of LH by AMHRII receptors on the surface of GnRH neurons. The level of AMH is positively related to the level of the hormone LH in women with PCOS, and excess LH increases the secretion of ovarian androgens by theca cells. This shows that in this syndrome there is a positive feedback loop between AMH, GnRH, and LH (Cimino et al., 2016)

The increase in the level of AMH in the serum of women with PCOS is a result of an increase in androgen in the small antral follicles, and that each follicle produces a normal amount of AMH, and it can be speculated that since AMH inhibits the activity of FSH, which It stimulates the activity of aromatase in human granulosa cells. It may also be responsible for the decrease in the activity of aromatase in granulosa cells in women with this syndrome and contributes to an increase in the level of androgens (Obeid et al., 2015).

Conclusion

It is concluded from the current study that PCOS has a significant effect on the rise in levels of adipokines (chemerin and visfatin) and anti-Mullerian hormone (AMH) in the serum of women with this syndrome. This shows the extent of the role of adipokines in human fertility and reproductive function, especially in the physiological function of the ovary. Therefore, these adipokines affect the regulation of the pituitary-gonadal axis or change the composition of ovarian steroids in women with this syndrome. We conclude from this study that chemerin, visfatin, and AMH can be used as a biomarker for early detection of PCOS and clinical signs such as infertility and hyperandrogenism in women with polycystic ovary syndrome.

Data availability

The data supporting the findings of this study are available within the article [see Results and discussion, Table 1, 2, 3].

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