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THE ROLE OF SESTRIN 1 IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

***Purpose**: Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder that affects at least 10% of women of reproductive age. Cystic ovaries, low or absent ovulation, and high circulating testosterone levels are the group of symptoms that define polycystic ovary syndrome (PCOS). The study aimed to investigate whether sestrin 1 can serve as a prognostic indicator in polycystic ovary syndrome.*

***Subjects and Methods:** The study included 100 women of ages between 18 and 44 years old, involving 70 PCOS patients and 30 healthy women as a control in reproductive age. The sample was selected from the reproductive fertility consultant of the Gynecological and Obstetric Teaching Hospital, Kerbala Health Directorate, Iraq and the College of Applied Medical Sciences, University of Kerbala, Iraq during the period from October 2022 to April 2023. The Rotterdam criteriOn-2003 was presumed to PCOS females.*

***Results:** The results showed a highly significant decrease in women with PCOS in contrast to women without PCOS. According to BMI, it had high significance in the overweight at (P =0.001), whereas in the obesity at (P= 0.004) and normal weight at (P= 0.004). According to age, it was highly significant in the age group (18_23), while in the age group (24_29) at (P =0.000) and age group (30_35) at (P=0.006) Whereas age group (36_41) at(P=0.274).*

***Conclusions:** It is concluded that reduced serum sestrin 1 level may have potential as a new PCOS diagnostic biomarker.*

INTRODUCTION

PCOS is a long-term hormonal disease that impacts the reproductive system in 10 to 15% of women globally(Barrea *et al*., 2023). If at least two of the three criteria are met, a woman is confirmed with PCOS: elevated androgen activity, polycystic ovarian morphology, or oligo- or anovulation (Adone & Fulmali, 2023) To preserve fertility, the ovary and the menstrual cycle must function normally, which is greatly influenced by hormones. A cyst can develop inside an ovary's sac if there is a persistent imbalance in a woman's hormone levels, which will affect how her ovaries operate. In contrast, androgen, a male hormone, is raised above normal in females who have PCOS (Ajmal *et al*., 2019). In patients with polycystic ovarian syndrome (PCOS), levels of the hormones follicle-stimulating hormone (FSH), luteinizing hormone

(LH), and gonadotropin-releasing hormone (GnRH) are consistently abnormal. which together cause ovulatory failure and increase androgen releases (Y. Xu & Qiao, 2022).

Numerous metabolic issues, including hypertension, diabetes of type 2, lipid disorders, cardiovascular disease, and atherosclerosis, are correlated with PCOS. PCOS, which affects 44–70% of adults, frequently manifests as resistance to insulin and hyperinsulinemia (Tefagh *et al*., 2022). A cytoplasmic protein belonging to a highly conserved family also known as PA26 gene relatives involved in growth arrest and DNA repair, including SESN1, is responsible for responding to DNA damage. All human tissues contain SESN1, but it's particularly abundant in the skeletal muscle, the heart, the liver, and the brain (Y. Chen *et al*., 2022). By regulating complexes 1 and 2 of the mammalian target of rapamycin kinases, SESTRINs regulate cellular homeostasis (Ding *et al*., 2019). Sestrin deficiency was found to speed up several processes, including mTORC1 activation, redox dysfunction, aging, fat storage, insulin resistance, muscle deterioration, cardiac failure, mitochondrial diseases, and cancer (M. Kim *et al*., 2021). Anovulatory infertility may eventually develop from GC-related dysfunctions that cause abnormal folliculogenesis (Naji *et al*., 2017)

Particularly, PCOS patients exhibit enhanced GC proliferation. Sestrin 1 downregulation may be a unique PCOS therapy option. Sestrin 1's function in controlling PCOS, however, is still not well studied (X. Xu, Song, *et al*., 2021).

METHODOLOGY

Patients Group

Samples of whole blood from 70 PCOS women Age of childbearing (between the ages of 18 and 44) The information was collected from reproductive infertility specialists of the Kerbala health directorate of Iraq's teaching gynecology and obstetrics hospital. There was extensive questioning on the subject, as well as laboratory tests. To learn more about the patients, a questionnaire was designed, such as age, weight, height circumference, fertility, hirsutism, menstrual regularity, and. Body mass index (BMI) and other physiological measurements were taken in these investigations.

Control Group

Thirty Women who appeared to be in healthy condition and whose ages ranged from (18 to 44 years). They have a normal menstrual cycle & have healthy ovaries, according to gynecologists' observations, weight, age, height, measurements, and hirsutism, together with regular menstrual cycles and fertility were all questioned for the control group. Not smokers, those without a history of renal, liver, cancer, stroke, autoimmune illness, any acute or chronic disease, diabetes, type 1 or type 2, or any sort of cerebrovascular accident. The study's healthy and ill participants were all married or not married.

Blood Collection

For blood collection, Needles and syringes 5ml were disposable. On day two of the cycle, vein punctures were used to collect blood samples from PCOS patients and control groups. At room temperature, the samples of blood were allowed to coagulate for 10–15 minutes. After dividing the blood into four equal pieces, we centrifuged it at 2000 x g for 10 to 15 minutes to separate the serum. luteinizing hormone (LH), Testosterone, follicle-stimulating hormone (Fsh), fasting blood insulin as well as sugar levels that were all assessed promptly by validated assays of respective serum hormones. The rest were stored in a deep freezer at a temperature of -80 degrees ºC. until levels of sestrin 1 are examined by (ELISA) kits.

Exclusion Criteria

None of the participants in this study were smokers. Patients with congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, diabetes mellitus, thyroid disorders,

hypertension, medication for preventing pregnancy, or the absence of polycystic ovary syndrome were also excluded from the trial, as were those with cancer

Diagnostic Test (Human Sestrin-1（SESN1）)

The quantity of Human SESN1 in the sample is determined, and solid-phase antibody is produced by coating microtiter plate wells with Purified Human SESN1 antibody, introduces SESN1 into well, as well as Human SESN1 antibody is conjugated to horseradish peroxidase (HRP) to create an antigen-antibody-enzyme complex. Finally, after being washed thoroughly, the substrate will turn blue when the TMB substrate solution is introduced. To inhibit the HRP enzyme-catalyzed reaction, a sulphuric acid solution is added.

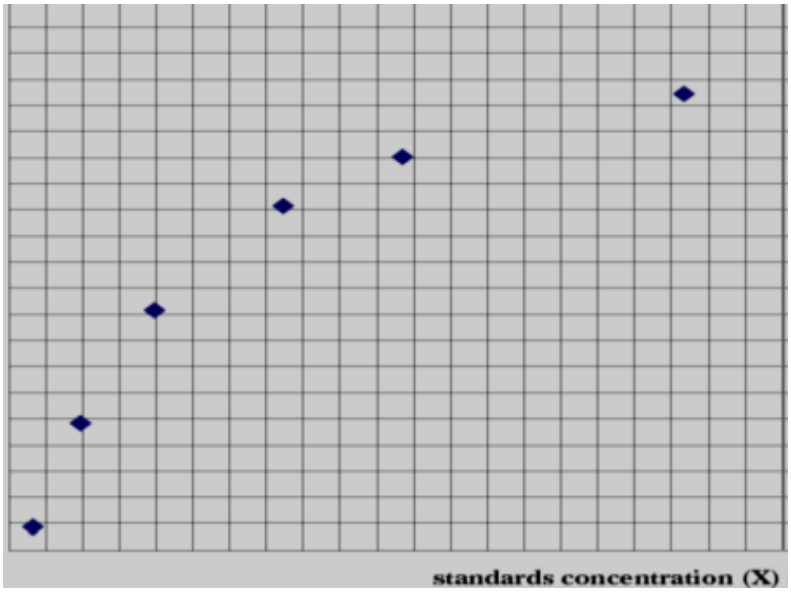

Figure (1): *Typical standard curve for human sestrin 1*

RESULTS AND DISCUSSION

The study involved 100 women between the ages of 18 and 45 who were of reproductive age. They were divided into two groups: 30 women who appeared to be in good health and 70 PCOS women who suffering from clinical signs that included an irregular menstrual cycle, acne, hirsutism, alopecia, an aberrant hormonal value (ratio LH/FSH), and an ultrasound imaging test, can be used to investigate this patient population

BMI in Polycystic Ovary Syndrome

Obesity considerably enhances the prevalence and severity of insulin resistance, even though PCOS is linked to it independently of obesity as a result, PCOS also raises the possibility of developing T2D. The effects of compensatory hyperinsulinemia on the ovary are what essentially drive the hyperandrogenic and reproductive characteristics of PCOS(Barber & Franks, 2021).

Since the body cannot properly use insulin, approximately 70 % of women who have PCOS have insulin resistance. It should be noted that obesity is the primary cause of insulin resistance and that both of these conditions increase the risk of developing diabetes(Ali, 2021).

Biochemical parameter in patients with Polycystic ovary syndrome

Table (2): The Biochemical parameter in patients with Polycystic ovary syndrome

LH	**patient**	9.82	5.87	.70	.000
	control	4.80	1.66	.30	
FSH	**patient**	5.13	1.29	.15	.000
	control	6.42	1.98	.36	
Testosterone	**patient**	2.55	1.17	.14	.000
	control	1.52	.72	.13	
E2	**patient**	54.46	16.69	1.99	.013
	control	97.51	140.66	25.68	

Sestrin 1 levels in Women with PCOS & a Healthy Control Group

Table (3) compares the levels of sestrin 1 in each of the research groups. According to the results, PCOS women's levels of sestrin1 are significantly lower than those of the control group.

Table (3) Comparison of serum sestrin 1 level in the study group

Parameter	Control group Mean ± SD	Patients group Mean ± SD	P- value
Sestrin 1	6238.511± 1416.13_	4281.721±1296.25	0.000

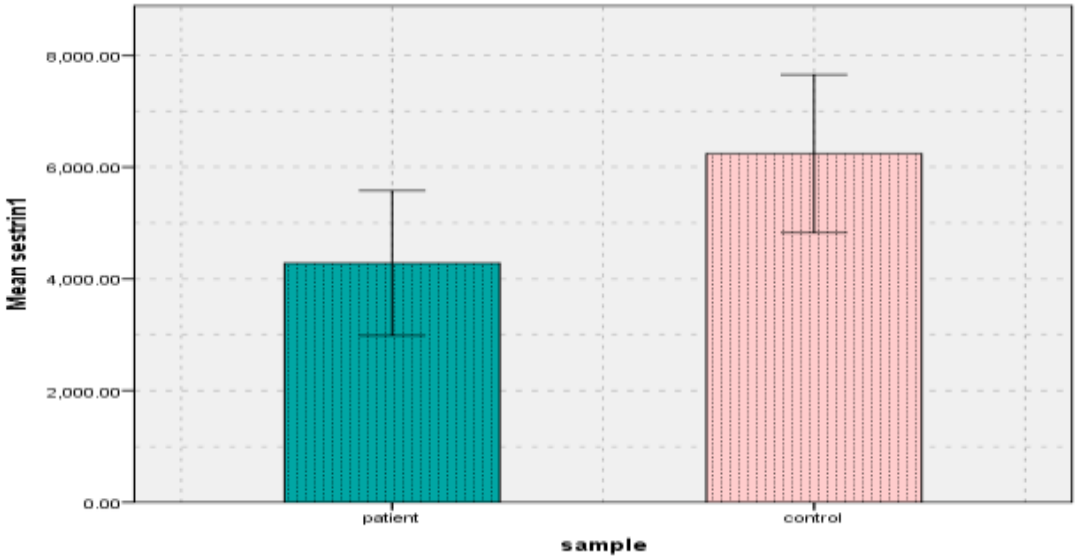

Figure (2): The mean levels of sestrin 1 found in women who have PCOS compared to a control group of women

A prevalent reproductive endocrine condition called polycystic ovarian syndrome (PCOS) affects at least 10% of women of reproductive age. At least two of the three cardinal characteristics of PCOS, including cystic ovaries, oligo- or anovulation, and hyperandrogenemia (high circulating androgen levels), are frequently present(Coutinho & Kauffman, 2019). Symptoms of (PCOS) involve menstrual cycles irregular, increased hair growth, infertility, and difficulties getting pregnant. Anxiety, desperation, and distorted body images, have all been related to PCOS (Louwers & Laven, 2020).

The pituitary gland is normally stimulated to release gonadotrophins, such as LH and FSH, by the hypothalamus's pulsatile release of the gonadotropin-releasing hormone. Luteinizing hormone stimulates the generation of androgens by acting predominantly on ovarian theca cells that have LH receptors (Ashraf *et al*., 2019). FSH acts on the ovarian granulosa cells and alters the androgens produced in the theca cells into estrogens, primarily estradiol, which is essential to the formation of follicles (T. Liu *et al*., 2021). Patients with PCOS demonstrate Luteinizing

hormone levels are higher, which encourages ovarian theca cells to secrete androgens (Szeliga *et al*., 2022).

An imbalance in gonadotropin-releasing hormone (GnRH) secretion causes a greater proportion of luteinizing hormone to follicle-stimulating hormone (FSH). The aberrant feedback process that led to an increase in LH release was triggered by ovarian estrogen (Saadia, 2020). Meiotic maturation to the Oocyst is a critical step in the progression of the Oocyte. The LH surge during this procedure causes oocytes to resume meiosis and complete the first meiotic division by releasing them from meiotic prophase arrest (Arroyo *et al*., 2020). In a normal ovarian cycle, the dominant follicle is the only one that responds to the peak surge of luteinizing hormone. Early terminal differentiation was seen in tiny follicles that are antral from a set of females with PCOS-related anovulation in response to increased LH levels (Szeliga *et al*., 2022).

Ovarian theca cells expand (hyperplasia) as a consequence of elevated amounts of the luteinizing hormone (LH). As a result of this process, a string of pearl-like cystic structures called follicles forms along the border of the ovary. The theca cells in the ovaries are responsible for this condition, which occurs naturally. This condition is characterized by abnormally active theca follicles, especially through pre-entral as well as Antral stages of a woman's menstrual cycle. Because of an increase in the number of follicles as well as the release of essential enzymes involved in the process of androgen production, an oversupply of androgens results (Singh *et al*., 2023).

The levels of FSH could be increased, decreased to lower than their typical levels, or stay stable in patients of condition (PCOS) (Mohammed & Qasim, 2021). An imbalance along the hypothalamic-pituitary-ovarian (HPO) pathway is thought to be able to arise, according to the beliefs of several experts. because of neuroendocrine system instability, leading to gonadotropin overproduction. As GnRH levels rise, LH production is favored over FSH production, causing the proportion of LH to FSH. to rise dramatically (Walters *et al*., 2018). Patients with polycystic ovarian disease do not ovulate because of a high LH/FSH ratio. The ratio of LH, to FSH. ranges from 1 to 2 in women who are normally healthy. The ratio is reversed for women suffering from PCOS and in certain instances, the number can even approach 2 or 3(Saadia, 2020). Recurrent, cyclical lowering of LH (GnRH) pulsatility is brought on by cyclic (luteal) rises in progesterone in ovulatory women. PCOS is characterized by the presence of persistent oligoovulation or anovulation. Despite this, women who have PCOS almost never experience the post-ovulatory surge in progesterone which is typical of women who have regular menstrual cycles (Blank *et al*., 2006). The steadily increasing GnRH pulse rate, which is a hallmark of PCOS in adult women may be caused by decreased levels of progesterone that are related to anovulation. In line with previous results, elevated LH levels also suppressed progesterone levels in our investigation(Malini & George, 2017).

Free Testosterone is a type of androgen that is biologically active. It is a chemical that is secreted, and its origins may be linked to both the ovary and the adrenal zona fasciculate. Only 1% unbound amounts of testosterone are present, with most of it connected to albumin and sex hormone-binding globulin (about 33% and 66%, respectively) (Sun *et al*., 2021). It is interesting to note unbound testosterone is the only type of hormone with biological activity, while testosterone bound to proteins is inactive form**.** PCOS patients who have elevated the amount of free testosterone as well as the free androgen index (FAI) have been diagnosed with the condition known as hyperandrogenism (Maksym *et al*., 2019). Hyperandrogenism observed in individuals having polycystic ovary syndrome (PCOS) is almost always generated by a rise in the amount of androgen. That has worsened by GnRH-dependent LH secretion, which increases androgen synthesis in theca cells. while suppressing follicular maturation, leading to

an abundance of small antral follicles and anovulation. Although the exact cause of follicle arrest is unclear, an excessive amount of androgens, LH, and insulin are probably secreted(Stener-victorin, 2022). Hyperandrogenism is considered to be the most significant clinical feature of PCOS. PCOS affects around 80 percent of all females, with high levels of androgenic symptoms or indications, for example, hirsutism, and skin conditions such as acne or hair loss, according to estimates(Sanchez-garrido & Tena-sempere, 2020).

Estradiol (or 17-estradiol) is sometimes referred to as "estrogen" due to its physiological importance and prevalence throughout reproductive years. The corpora lutea and the ovarian follicles' granulosa cells are the principal secretors of estradiol, the main circulating estrogen in humans(Fuentes *et al*., 2019). In polycystic ovary syndrome, the granulosa cells can't develop into follicles, therefore they don't make much estrogen. The inability to ovulate may be the primary due to infertility in women with PCOS. (Khattak *et al*., 2022). The current finding demonstrated that individuals who had PCOS had significantly lower levels of sestrin1 in contrast to females without PCOS who were in good health. Autophagy was inhibited when Sestrin 1 was knocked down, which led to an increase in reactive oxygen species and the death of cells. These modifications may have prevented the onset and progression of PCOS.

Sestrins antioxidant properties and processes have been studied (Rhee & Bae, 2015). There are two principal mechanisms through which sestrins exert their antioxidant action. In the initial stage, sestrins promote Keap1's p62-dependent autophagy, which in turn increases Nrf2 signaling and, as a result, the production of antioxidant enzymes (Xu *et al*., 2021). Sestrins in the second inhibited the buildup of reactive oxygen species by blunting mTORC1 activation. Insulin resistance, a key pathophysiological component of PCOS, can be caused by overexpression of the mTOR pathway(Liu *et al*., 2018). Another study supports that Sestrin1 levels were significantly lower in people with obesity(Nascimento *et al*., 2013).

CONCLUSION

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder that affects at least 10% of women of reproductive age. Cystic ovaries, low or absent ovulation, and high circulating testosterone levels are the group of symptoms that define polycystic ovary syndrome (PCOS). The study aimed to investigate whether sestrin 1 can serve as a prognostic indicator in polycystic ovary syndrome. It is concluded that reduced serum sestrin 1 level may have potential as a new PCOS diagnostic biomarker.

CONFLICT OF INTEREST:
The authors declare no conflict of interest.

FUNDING:
The study self-funded.

ETHICAL CLEARANCE:

Permission was taken from the concerned authorities. Patients were also informed about the purpose of the study and they all gave their consent to participate in the study.

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