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Polycystic Ovarian Syndrome: A Narrative Review Article on Serum Markers in Pcos

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

PCOD is a heterogeneous illness characterized by clinically or biochemically excess androgen, dysfunction in ovulation, and polycystic ovaries that is caused by a complicated hereditary disease.
Poly-cystic ovary syndrome (PCOS), affecting 10 to 20% of premenopausal females, is a common heterogeneous disorder depending on diagnostic criteria of high serum levels of androgen concentrations, and infertility, irregular menstruation, provided that precise diagnosis such as hyperprolactinemia and inbred adrenal hyperplasia have been debarred. In recent years, the international agreement has favored the adoption of the Rotterdam criteria for mature women's diagnosis. During pubertal development, non-uniform menses, chronic anovulatory cycles, multi-follicular ovary shape, and moderately increased blood androgen concentrations are common.
It's difficult to establish a diagnosis in adolescent females since there's a lot of overlap between typical pubertal milestones and PCOS clinical characteristics. Insulin resistance, hyperinsulinemia, and obesity are all typical symptoms of PCOS, however, they aren't diagnostic.
Impaired glucose tolerance, which leads to insulin-dependent diabetes mellitus, insulin resistance, dyslipidemia, increased blood pressure, endometrial cancer, hyperinsulinemia, obesity, alcoholic independent fatty liver, and sleep apnea are among the comorbidities linked with PCOS.

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Depression and poor conditions of life are also prevalent problems. Preliminary detection of PCOS in teenage females is critical.
The goal of this article is to offer a summary of serum indicators and evidence for several serum markers used to diagnose PCOS.

Keywords: Insulin resistance; Poly-cystic ovary syndrome (PCOS); fertility; irregular menstruation.

1. INTRODUCTION

PCOS is a diverse syndrome characterized by clinically and biochemically excess androgen, dysfunction in ovulation, and polycystic ovaries, all of which are caused by a complicated hereditary disease [1].

Polycystic Ovary Syndrome (PCOS) is a multiplex hereditary set-up of endocrine that affects many women. Various diagnostic norms have been proposed, however, the following two are the most often suggested: The 1991 NIH Conference on PCOS recommended that the existence of hyperandrogenism, oligoovulation along with hyperandrogenemia, followed by the ruling out any other medical condition, be considered important for evaluating PCOS, or that the presence of any two of the three symptoms listed above, followed by the excluding the other endocrinopathies, be accepted evaluating examination for PCOS, as recommended by the broader 2003 Rotterdam consensus.PCOS impacts roughly 10% of women worldwide, according to the Rotterdam criteria, however, it hits a higher percentage of women [2,3,4]. PCOS is the most frequent human condition, as well as the commonest single disorder affecting reproductive-age women. Previously thought to be primarily relevant in occasion of conception, PCOS has currently been associated with a number of lengthy hazards, along with with cardiovascular disorder, diabetes mellitus, hyperinsulinemia, and other morbidities [5].

There is no absolute method for describing all of the intramural and extramural symptoms linked with this complex metabolic illness. However, research has given a general grasp of the disorder's aetiology. The fundamental abnormalities in PCOS patients can be seen in two areas of the body: resistance to insulin and relative LH/FSH levels [6].

Insulin resistance occurs in many PCOS patients, which means that their body's cells do not acknowledge the insulin hormone and hence do not absorb glucose. Because glucose isn't used to make energy, it's accumulated in the body, which leads to increase body mass. An elevated level of insulin in the body forces the ovaries to generate more androgen over time. This causes oligo-ovulation (non-uniform ovulation) or lack of ovulation. Insulin resistance is tissue-selective because it affects some of the usual insulin-targeted organs, being adipose tissue, muscles. In muscles, serine phosphorylation of the insulin sense organ and insulin receptor substrate 1 (IRS1) is greatly exceeded, disrupting insulin signaling and activating the mitogen-activated protein kinases MEK1 and MEK2. Organs, such as the ovary, are unaffected by insulin resistance [7,8].

2. METHODS

2.1 Data Sources

2.1.1 Search strategy and selection criteria

We reviewed key papers and also undertook searches of electronic databases such as PubMed, Medline, LILACS, and CENTRAL. We excluded non-English articles, case reports and studies.

The search items for PubMed were ‘Polycystic Ovary Syndrome’, along with ‘Serum Markers in Polycystic Ovary Syndrome''Increased Hormone Levels in PCOS'. The South Asian database of Controlled clinical trials was searched by use of the term ‘PCOS’.To create the most number of articles, the keywords were utilized in various combinations. Relevant article references were also evaluated and added if they were relevant.

2.1.2 Polycystic ovary syndrome serum markers

Evaluation of polycystic ovarian morphology (PCOM) for PCOS diagnosis involves substantial variability, also with the most modern ultrasound techniques. As a result, objective parameters are required, and serum marker levels may be beneficial in the diagnosis of PCOS [9].

1. Androgens:

The increased production of androgen from the ovary found in PCOS is largely due to amplified androgen synthesis by follicular theca cells, which is responsible for overexpression of numerous genes encoding steroid enzymes1 [10,11,12]. As high androgen levels are the most consistent symptom of PCOS, hyperandrogenism is the key component. The majority of patients (60%) have hyperandrogenism [13,14]. In females with hyperandrogenic PCOS, and the pro-androgens androstenedione (A4), serum levels of testosterone (T) and 'dehydroepiandrosterone sulfate' (DHEAS), additionally the enzyme which are needed to convert pro-androgens to bioactive 'androgens, 3-hydroxysteroid dehydrogenase (3-HSD)', are all increased [14,15]. Insulin resistance and hyperinsulinemia can cause an elevation in free androgens, as well as unfavorable metabolic profiles, by decrement in sex hormone-binding globulin levels [16]. Endogenous adrenal androgen hypersecretion in "congenital adrenal hyperplasia" or "exogenous testosterone" treatment in "female-to-male transsexuals" exposes women with ovarian PCOS morphological characteristics of extended, multi-cystic ovaries and theca interstitial hyperplasia to higher levels of androgens [17]. Furthermore, theca-interna cells derived from PCOS affected ovary produce excess androgen in culture, which persists over time. These findings back up the theory that androgens have a part in the progression of PCOS ovarian traits [18].

2. Luteinizing hormone Vs Follicle Stimulating Hormone Ratio (LH: FSH)

Ovulation is aided by the hormones: LH, FSH. The pituitary gland situated in the brain produces both LH and FSH. LH and FSH levels typically range from 5 to 21 mIU/ml at the start of the cycle. During the initial part of their cycle, most females have roughly equal quantities of LH and FSH. While many females with PCOD have LH, FSH levels in a 5-21 'mIU/ml' range, LH levels of them are often three or four times higher than their FSH levels. Women with PCOS, for example, often have 'LH' level of around '19 mIU / ml' and an 'FSH level' of around '6 mIU/ml'.An increased LH vs FSH ratio, often known as a 4:1 ratio, describes this scenario. The alternation in the 'LH vs FSH' ratio is ample to cause ovulation to be disrupted. As it was once thought to be an essential factor in detecting PCOD, now it is thought to be reduced so, but it is still valuable when looking at the big picture.

The HPOA AXIS has been implicated in the development of polycystic ovarian disease. The release pattern of "gonadotrophin-releasing hormone (GnRH)" is disturbed, resulting in a rise in the ratio of LH to FSH release. The abnormal feedback loop that resulted in an increase in LH production was caused by ovarian estrogen. In well to do women, the ratio of LH to FSH is between one and three. This ratio is inverted in women with the polycystic ovarian disorder, and it can reach as high as 2 or 4 in some cases. Ovulation does not occur in polycystic ovarian disease patients due to a high LH/FSH ratio [19].

3. Testosterone

There are raised levels of testosterone. Given the challenges with many of the tests used to measure free testosterone, the total amount of testosterone is likely to be more trustworthy. In PCOS, testosterone levels may be normal or not. Oral contraceptive pills diminish total levels of testosterone, making interpretation problematic in this situation. The average testosterone level in PCOS is 160 ng/dL (6.2 nmol/L). When testosterone levels reach 250 ng/dL (6.8 nmol/L), an adrenal or ovarian tumor should be considered [20].

4. Anti- Mullerian Hormone(AMH)

AMH, is released by growing ovarian antral follicles. Because it corresponds with sub-total quantity of antral follicles on both ovaries, serum Anti-Müllerian hormone is now presented as a serum marker for 'PCOS detection'. Although AMH is noninvasive and constant throughout the menses cycle, AFC and ovarian complexes are better estimated throughout the phase of follicle . A recent theory proposes that AMH, in place of being only a measure of count of ovary follicles, may be allowed to play a significant role in the aetiology of PCOS as an indicator of endocrine. A fraction of 'gonadotropin-releasing hormone (GnRH)' neurons manifests the 'AMH receptor', and AMH enhances neuronal activity of GnRH. Changes in GnRH pulsatility affect pituitary gonadotropes, and raised 'GnRH' pulsatility is correlated to LH-overriding gonadotropin production, whichever is frequent, though not general, characteristic of PCOS. PCOS ladies have the greater amounts of 'AMH' than complementary controls. As people become older, their AMH levels drop, which corresponds

to improvements in several PCOS clinical features. Females with PCOD who are anovulatory, for example, may have their cycles of menstruation return to normal as they become older. Even in women without PCOS, cycle length shortens as they get older prior to the climacteric, leading to a decrease in ovarian reserve indicators [21].

5. Prolactin

Mild hyperprolactinemia has been documented in between 5% and 30% of PCOS patients. Prolactin levels are usually only around half of what they should be. Furthermore, hyperprolactinemia is usually temporary, with only about 3% to 7% of hyperprolactinemic PCOS individuals experiencing consistently increased prolactin levels. As a result, PCOS and hyperprolactinemia are currently thought to be separate illnesses. If re-sampling does not result in normalizing, a search for additional explanations should be made (Incorporating magnetic resonance imaging of the pituitary). On ultrasonography, patients with prolactinomas may have polycystic ovaries [20].

6. Dehydroepiandrosterone-sulfate ('DHEA-S')

'DHEA-S', aka 'dehydroepiandrosterone', is some other male hormone that is also found in all women. The adrenal gland produces the androgen DHEA-S. Women's DHEA-S levels generally vary from '35 to 420 ug/dl. Most women with PCOS have DHEA-S levels beyond '250 ug/dl.

DHEA-S levels in PCOS might be normal or slightly elevated. The existence of an adrenal tumor is indicated by DHEA-S levels of 700 g/dL (22.7 mol/L) [20].

7. Thyroid Stimulating Hormone (TSH)

The thyroid gland, which is situated in the neck, produces Thyroid Stimulating Hormone (TSH). TSH levels in PCOS women are usually within normal limits (0.5-3.9 uIU/ml). TSH levels are examined to eliminate other problems including an inactive or agitated thyroid, which can cause uneven or missing menses as well as anovulation.

8. Endometrial Resistance of Progesterone

The endometrium of a lady presented with PCOS shows signs of progesterone resistance, which is characterized as a reduction in the responsiveness of target tissue to bioavailable progesterone. The reality that the endometrium of a lady with PCOS is broader than that of a healthy woman indicates that they have an irregular menses cycle and anovulation, resulting in little or no 'P4 production'. Despite the fact that gene expression study of PCOS endometrium discloses resistance for progesterone and possible susceptibility genes in PCOS women, the molecular mechanisms behind progesterone resistance of endometrium or sensitivity in all of these people are unclear [22].

9. Estrogens

Estrogen is the hormone of females that is produced mostly from ovaries, but also in minor amounts from the adrenal gland. The more active estrogens in the body of the female are estradiol. Enough estrogen must be present to interact with progesterone to encourage menstrual bleeding. The majority of PCOS women are astonished to find out that their estrogens levels are within the normal limits (between '25 and 65 pg/ml). This might be because of the high amounts of insulin and testosterone developed in PCOS women being converted to estrogens on occasion.

10. Insulin Resistance

Archard Thiers syndrome, often known as diabetes of the bearded ladies, was initially described in 1920 as the In postmenopausal women, diabetes mellitus can coexist with clinical symptoms of androgen excess.Insulin resistance has been linked to a range of reproductive issues in PCOS women. Insulin circulating levels in healthy people range from 6 to 15 IU/ml. The amount rises to 24 IU/ml in women with PCOD. Hyperinsulinemia is thought to have a huge role in the progression of PCOS and is linked to higher level of androgen. Insulin resistance, diabetes Mellitus, and other diabetic complications can all be caused by increased androgens in PCOS women. Insulin receptor (IR) is present in the theca cells of the ovary and osteoblasts of the bone. Hyperinsulinemia is observed to be a cause of hyperandrogenemia since insulin can straightly stimulate increased androgen production from theca cells. Insulin signal transduction is thought to involve a number of signaling pathways. Insulin activates Phosphoinositide 3 kinase, Protein Kinase C, and Phosphoinositide Dependent Kinase 1, enabling steroid regulatory element-binding protein 1 to translocate from the cytoplasm to the

nucleus. SREBP-1 is a transcription factor involved in fatty acid production. Insulin controls SREBP activation and translocation from the cytoplasm to the nucleus through signaling through the "PI3K/Akt "and "Mammalian Target of Rapamycin" pathways. In women with or without PCOD, the levels of "sex hormone-binding globulin" are closely related to the amount of circulating insulin or the degree of insulin resistance, implying that insulin has a suppressive impact on SHBG. Treatments aiming at reducing insulin resistance resulted in lower androgen levels [23].

Hyperinsulinemia can occur as result of both decreased insulin clearance and increased insulin production. Because insulin clearance is receptor-mediated, and acquired deficits in receptor number and/or function are common in insulin resistance related to hyperinsulinemia and/or hyperglycemia, decreased insulin clearance is frequently evident in insulin-resistant states [24].

2.1.3 Insulin resistance has some new markers

Despite the fact that different tests for detecting insulin resistance exist, new markers are urgently needed to generate a more dependable evaluation of insulin metabolism. Too far, a few new proteins have presented as surrogate indicators for determining the resistance of insulin. In the sections below, we give a brief overview of markers that have recently been investigated as biomarker\ indicators of metabolic state.

*AdipoCytokines
*Kisspeptin
*Copeptin
*Irisin
*Ghrelin
*PAI-1
*Zonulin [25]

1. Sex Hormone - Binding Globulin in PCOD:

- Levels of SHBG in Adult PCOD females:

Metabolic syndrome and PCOS are connected, as stated by a current systematic review and meta-analysis of registered clinical trials. Intriguingly, the meta-analysis discovered that obesity-related metabolic abnormalities were linked with considerably reduced SHBG levels but not with indices of hyperandrogenism in women with PCOS, indicating that decreased SHBG develops before increased androgens in PCOD. In addition to this , treatment intervention with metformin, myo-inositol, and D-chiro-inositol raised blood levels of SHBG and was linked to better function od ovaries and metabolism in women with PCOD.

- SHBG Levels in Youth having PCOS:

Obesity has skyrocketed among teens and children throughout the world as a result of westernised lifestyles. Obesity has an effect on females' development throughout puberty and raises the chance of PCOS. Childhood obesity is the first symptom of insulin resistance and a precursor to PCOS, according to clinical observation. The link between obesity and PCOS is partly explained by obesity's detrimental impact on SHBG production and secretion, which increases testosterone bioavailability. PCOS symptoms frequently appear throughout adolescence, implying that puberty/adolescence is a critical developmental stage in the development of PCOS pathophysiology. However, because of changes in physiology associated with puberty coincide with those associated with PCOS, a diagnosis of PCOS in teenagers is still debatable. Nonetheless, the severity of pre-pubertal obesity raises the risk of PCOD. PCOS was shown to be prevalent in >5, >10, and >20 percent of overweight, moderately obese, and severely obese females, respectively, in a population-based research of teenage girls (ages 15–19 years). Furthermore, decreased blood SHBG levels have been linked to metabolic syndrome as a risk factor for PCOS in teenagers.As a result, SHBG levels might be a helpful and practical test for detecting PCOS in young women, particularly teenagers [26-28].

3. SUMMARY

PCOS a widespread medical condition of the endocrine affecting the feminine reproductive system, and it is affected by biochemical, genetical, and surrounding factors. Long standing distress like diabetes and cardiovascular disease are led by pcos. ‘PCOS’ symptoms include rapid increase of body weight, hormonal imbalances, hirsutism, oligo or anovulation, poly cystic ovaries, hyper insulinemia, and hyper androgenemia (excess testosterone). Insulin resistance along with luteinizing hormone and also the follicle-stimulating serum hormone levels are connected

to increased ‘androgen’ and ‘testosterone’ synthesis; increased levels of LH than that of FSH also contribute to anovulation or oligo-ovulation, as well as difficulty conceiving.

PCOS is diagnosed by ruling out all further feasible endocrinopathies in the existence of androgenemia, androgenism, and an/oligoovulation. Inspite of the fact that some locations depend on the look of the ovaries to diagnose, other indicators such as genes, proteins, and enzymes can also be employed. The genetic markers studied include those involved in controlling insulin action and androgen production, and the 42 genes have been identified as being linked to PCOS. These genetic markers, on the other hand, aren't functional for preliminary detection and can only be used to certify PCOS in those who have so far displayed the symptoms. Proteins and enzymes indicators are often utilised for better prognosis and monitoring of the patients in order to avoid the progresion of PCOS consequences likely the cardiovascular disease (CVD). Insulin resistance and the development of PCOS have been linked to proteins present in adipose tissue. Enzymes and proteins, on the other hand are unstable and quickly degraded, which has hampered thorough study on them. As a result, a multi-factor study is required to diagnose PCOS.

4. CONCLUSION

Metformin is now recommended patients suffering from pcos since it has been shown to modulate the menstruation and boost conception rates in both non-androgenic and androgenic types of the condition. The injection of gymnemic acid, myo-inositol and L-methylfolate, according to a recent study, results in a substantial reduction in levels of testosterone, particularly in the people who are obese or overweight patients. Above all of this , because PCOS patients have a slower metabolism, To avoid the obesity, diabetes, CVD, and other all of the morbidities, they should maintain an active lifestyle.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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