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WOMEN'S PCOS: SIGNS, BIOMARKERS, CARE, AND INFERTILITY

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Abstract

PCOS, also known as polycystic ovarian syndrome, is a serious condition that has a negative impact on women's health, particularly when levels of "sex hormones" such as progesterone and oestrogen are high. Smaller cysts develop as a result of these unique hormone changes. The menstrual cycle, heart function, appearance, and pregnancy may all be affected. Menstrual irregularities, increased hair growth, acne, an increase in body weight, anxiety and sadness, an issue with infertility, etc. are only a few of the symptoms. Infertility, hormonal imbalance, ovarian malfunction, and the quantity of cysts in the ovaries are some of the effects of having this particular condition. Despite the fact that there are a variety of medical approaches to treating PCOS, including some drugs (such as clomiphene citrate, metformin, myo-inositol, etc.), there is no known cure for the disorder's signs or symptoms, no known cause for its onset, and no accepted best course of action. Using information gathered from numerous research papers, it was discovered that analysing PCOS is a difficult undertaking because there are so many factors to take into account. Each article employs several standards and focuses on them. The issues brought on by PCOS will be examined in this review, and some solutions will undoubtedly be offered. With certain corrective actions, this problem—which is becoming more and more serious with time—can be solved. In the upcoming review, specific drugs will also be covered.

Keywords: Polycystic ovary syndrome (PCOS), menstruations, ovarian cysts, obese, hormonal imbalance, hyperandrogenism.

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Abbreviations

IVF- In Vitro Fertilization

HA- hyperandrogenism

PCOS- Polycystic Ovary Syndrome

ICSI- Intracytoplasmic Sperm Injection

IVM- In Vitro Maturation

OHSS- Ovarian Hyperstimulation Syndrome

IR- Insulin Resistance

OCP- Oral Contraceptive Pills

NAFLD- Non-Alcoholic Fatty Liver Disease

OGTT- Oral Glucose Tolerance Test

FSH- Follicle Stimulating Hormone

SHBG- Sex Hormone Binding Globulin

LH- Luteinizing Hormone

IGT- Impaired Glucose Tolerance

BMI- Body Mass Index

NADPH-NicotinamideAdenine Nucleotide Phosphate

OR- Odds Ratio

IGT - Glucose resistance

CC- Clomiphene Citrate

GnRH- Gonadotropin-Discharging Hormone

NIH- National Institute of Health

NASH- Nonalcoholic Steatohepatitis

Introduction

The endocrine and metabolic ailment polycystic ovarian syndrome, or PCOS, which causes enlarged ovaries with tiny cysts on the outside of the organ, has been described as a terrifying condition for women between the ages of 18 and 44 (Teede *et al*., 2010). This is a problem that every fifth or sixth woman on earth faces. It is an indication of excess androgen (specifically a male hormone) , ovulatory dysfunction , polycystic ovaries (Rutkowska & Diamanti-Kandarakis, 2016) .An irregular menstrual cycle , excessive hair growth , skin acne, dark patches on the skin , obesity , reproductive issues (Goodarzi *et al.,* 2011) and other symptoms are all signs of PCOS. When a hormonal imbalance affects a woman, it will interfere with the ovaries' normal operation, which causes a cyst to form in the ovary's sac . In order to achieve pregnancies linked to OHSS, patients with PCOS undergo IVF or ICSI . Additionally, the prevalence of NAFLD, a hepatic consequence of PCOS and the second most frequent cause of liver transplantation in the United States, is rising in women with this syndrome (Younossi *et al*., 2019) . However, it is still unclear what causes NAFLD. The exact causes of PCOS are still unknown, but a surge in patient testimony supports the idea that it is a complex, endocrine system-related disease with characteristics brought on by a number of genetic variables as well as by natural, predominantly health-related disorders that may contribute to hormone imbalance (Spałkowska *et al.*, 2018). In 2003, Kaleli B. and his team hypothesised that the genes CAP10, AR, cytochrome family (p450), insulin gene, alpha-ketoglutarate dependent dioxygenase (FTO), and FSHR are associated with PCOS . Visceral adiposity index and lipogenesis, which are related to IR, should be higher in females with PCOS. The fundamental issue with PCOS is obesity; although 50–60% of patients are overweight, this is not a requirement for the PCOS phenotype (Durmus *et al.,* 2016). Additionally, it plays a significant role in the quality of oocytes and the premature growth brought on by endoplasmic reticulum stress brought on by lipotoxicity, which goes hand in hand with mitochondrial malfunction and further promotes apoptosis .

Researchers discovered that the patients had thicker visceral belly fat layers than the controls in a study by Jena *et al.* (2018) that included 58 women who had just been diagnosed with PCOS and 40 healthy

controls with comparable ages and BMIs. In 200 obese women with PCOS and 100 controls of similar age and BMI, Cascella *et al.* (2008) found that high visceral fat was directly associated with IR. In another study, Tripathy *et al.* (2017) observed that PCOS patients had greater amounts of visceral fat and carotid intimal medial thickness when they were compared to 118 age- and BMI-matched controls. Androgen levels affect alterations in lipid profiles that are specific to phenotypes, according to Shaman *et al*. The new nomenclature for PCOS is Schlerocystic Pod and Multicystic Ovaries, according to Stein and Leventhal (2019).

The most recent studies show that moderate hypercholesterolemia affects PCOS-affected women and eventually raises BMI and IR levels (Sirmans & Pate, 2013). Additionally, there are various degrees of lipid accumulation in PCOS, which are often correlated with decreased levels of total saturated fats (TC), minimum lipoprotein cholesterol (LDLC), high-density lipoprotein (HDL-I) cholesterol (HDL-C), and triglycerides (TG), as well as increasing densities of lipoproteins (Bousmpoula *et al*., 2017). There are various degrees of lipid accumulation in PCOS as well, which are typically correlated with lower levels of total saturated fats (TC), minimal lipoprotein cholesterol (LDLC), high-density lipoprotein (HDL-I) cholesterol (HDL-C), and triglycerides (TG), as well as elevated densities of lipoproteins. In prepubescent mice fed a high-fat diet, induced metabolic and ovarian changes cause PCOS .IR, lipid-related dysfunction, and obesity in PCOS are all associated with hyperandrogenism. Clinical pregnancy rates are lower in PCOS-afflicted women in both scenarios, i.e., during synchronised and spontaneous ovulation cycles (Pasquali, 2003). Visfatin, an adipocyte hormone, stimulates glucose lipogenesis and mimics the hormonal effects of insulin, improving insulin sensitivity and lowering insulin and glucose levels.

Some of the novel methods used to treat PCOS includes leading a healthier lifestyle, taking allopathic medications, and using ayurvedic or plant-based medications. Simply put, lifestyle modifications refer to exercise, a change in diet, and weight loss. The allopathic medications include anti-androgens (Flutamide and Spironolactone), insulin-lowering medications (such as thiazolidinediones and metformin), and estrogen-progestin-based medications (oral contraceptives). Treatments using allopathic drugs are expensive and may have a number of side effects, including increased IR, weight gain, gastrointestinal issues, and irregular menstruation . (Marx & Mehta, 2003).The goal of the current review is to examine the aetiology and pathophysiology (i.e., why and how) of this disease, as well as the possibility of various allopathic medications, in order to provide the best source for PCOS management.

Literature review

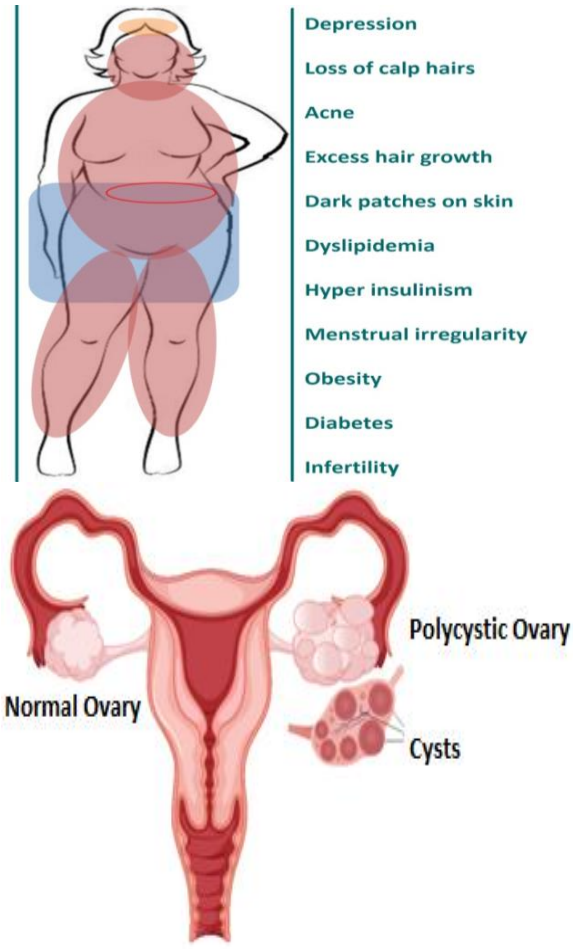
PCOS's History and Discovery

The first people to learn about PCOS were Stein and Leventhal. The Italian scientist Antonio Vallisneri made his discovery about a married woman with white ovaries the size of pigeon eggs in 1721. It didn't enter the NIH until 1990. A formal symptomatic criteria was proposed at a meeting on PCOS that was convened subsequently, and after a short while, it was heavily employed. Numerous tests have also been conducted in an effort to clarify the genesis of polycystic disease, which is the focus of many researchers. IR has been noted in female patients with this particular disease as well. Well, during the 2003 social event hosted in Rotterdam, the size and form of the ovaries were also included in the diagnostic criteria, as shown by an ultrasound report

(McKittrick, 2002) . Demonstrated Since 1935, it has been referred to as a syndrome in which one or both ovaries have numerous tiny lesions measuring between 2 and 9 millimetres in diameter, and at least one side produces ovarian follicles larger than 10 millilitres. Additionally, the review by the Excess Androgen and PCOS Society (AE-PCOS) in 2009 explicitly stated that, according to 18 published reports, the normal blood TT or FT was thought to be higher in approximately 50–60% of women with PCOS.

Symptoms

Menstrual irregularities, dark skin patches, acne, hair loss on the scalp, excessive hair growth, dyslipidemia , obesity , anxiety and depression, difficulties getting pregnant, diabetes , and hyperinsulinism are all symptoms of PCOS. Additionally, there are variations in menstruation, such as when it is overly heavy or when there are only patches. Because women who have thyroid disease also experience menstrual irregularities, thyroid-stimulating hormone levels are considered important. Acne and hirsutism are brought on by androgen hormone imbalances. The pancreas secretes insulin, which enables cells to digest sugar, the body's main source of energy . (Arentz *et al*., 2021) A surplus of insulin may enhance the release of androgen, which would therefore interfere with ovulation. According to research, women with PCOS have poor-quality irritation that stimulates the release of androgens from their polycystic ovaries, which can also lead to heart and vascular problems. While elderly women typically complain about metabolic issues, many young women lament infertility and its psychological repercussions. Some complications that occur during pregnancies in women with PCOS (e.g., infertility, pregnancy-induced hypertension , gestational diabetes , type 2 diabetes or prediabetes , abortions or premature births , NASH (an advanced form of a liver problem caused by fat accumulating in the liver) , and metabolic disorder (a number of problems including hypertension, being lethargic, increasing levels of glucose, and fluctuating blood pressure) Obesity and PCOS are associated, and the latter can exacerbate the condition's difficulties (Raphael *et al*., 1995). From the previously mentioned symptoms (Figure 1), we primarily focus on menstrual irregularity, infertility, and obesity.



Irregularities in menstruation

Teenagers frequently exhibit physiological menstrual instability. Oligomenorrhea is a good example. Additionally, dietary issues might affect a woman's menstrual cycle. Particularly in the first few years following menarche, periods may be infrequent, frequent, or excruciating. Approximately 25% of young women in Australia

experienced significant menstrual instabilities, which impacted their lifestyle (Kim & Lee, 2022). This was revealed by an Australian cross-sectional study. Additionally, there's a slight chance that you could get an ovarian illness. Furthermore, it has been suggested that the diagnosis of PCOS be postponed for at least two years after menarche in order to regulate period irregularity. It influences a woman's conceptual framework through multiple occurrences of estrogen or an unbalanced menstrual cycle.

Obesity :

Obesity is also seen as one of PCOS's most notable characteristics and a symptom of the condition. Being overweight is considered, as is the possibility of weight loss and instant weight gain due to hormonal changes, metabolism problems, diet-related issues, and an abundance of oestrogen..The fact that 80% of Americans and 50% of people outside the US are overweight shows that this statistic is dependent on hormone-restricting globulin (also known as SHBG), which causes PCOS-affected women's ovaries to produce more androgen (Legro, 2012). A significant amount of misery, pressure, and missed periods due to PCOS are also associated with obesity The bulkiness affects the upper portion of the body more than the lower, therefore, even though conceptual asymmetries are more common, women who are overweight have reduced odds of PCOS and hyperandrogenemia . In the upper portion of the body (referred to as the "android"), men have a lower fat-to-muscle ratio than women, who often gather fat in the lower portion of the body (referred to as the "gynoid"). In addition, one of the causes of women's heaviness is thyroid dysfunction.

Issues with conception

The disorder known as PCOS is undoubtedly one of the most significant causes of difficulties for women trying to conceive. The ovaries of a PCOS patient are larger than those of a healthy female. These larger ovaries may contain multiple times as many tiny blisters containing immature eggs. It causes a woman's body to produce more androgen hormone than usual. The development of male traits depends on androgens. Ovulation is the term for the process that occurs when a woman's levels of androgens are high enough to interfere with the development and normal production of eggs. If a solid egg is not released at this time, a sperm cannot fertilise it, indicating that the woman is not pregnant. PCOS can result in inconsistent menstrual cycles or missed periods. This might be one of the main PCOS symptoms that one experiences. While having PCOS, it is still possible to become pregnant and have a lot of children.

Causes

An excess of androgen is the main factor in PCOS in females. For females, the pituitary gland produces two important hormones: progesterone 2 and oestrogen 1.However, if they become unbalanced, it could cause issues for women and become a significant contributing factor to PCOS. Estrogen is the hormone in charge of the female reproductive system's development. Progesterone, on the other hand, has a role in pregnancy, embryogenesis, and menstruation.

Regarding PCOS, IR is crucial because it affects how insulin reacts, which can lead to hyperinsulinemia, a prominent component of PCOS. Type 2 diabetes and IR are most frequently experienced by 60–70% of women with PCOS [(Mu *et al.*, 2019) Up to 70% of women with PCOS also have dyslipidemia, which is indicated by hepatic fat in PCOS patients and a negative influence on plasma from the lipocytes in the focused fat .A study also summarised that there is a significant correlation between dyslipidemia and IR, with the amount of IR results being higher in women with a higher BMI compared to those with an average BMI . Furthermore, the accumulation of lipids and the degree

of obesity are the key indicators that assess metabolic aggravations associated with IR in PCOS patients at an early age . As one of the biomarkers of IR (HOMA-IR) in PCOS patients who are not responding to treatment, lipoprotein proportions, especially TG and HDL-C, closely correlate to insulin levels. On the other hand, the TG to HDL-C ratio can be used to predict IGT in young patients with PCOS . Women with PCOS who are suffering from IR have been found to have a higher average for bulk .Surprisingly, the instinctive assembly of intra-stomach cells may complicate fat digestion. In addition, women with PCOS who had greater body fat had a significantly lower rate of FFA concealment than the healthy controls , and emphasising fats encouraged the lipolysis of highly unsaturated fats . Additionally, increased lipolysis exhausts insulin's capacity to function in fat tissue . Higher nicotinamide adenine nucleotide phosphate oxidase activity reactivated by FFAs and the resulting reactive oxygen species may promote IR in obese women with PCOS. BMI and IR have a tight relationship. It is, however, still present in ideal-weight PCOS-affected women .Additionally, IR has been discovered in thin PCOS women . By enhancing lipotoxicity and encouraging FFA uptake in intra-abdominal adipocytes and non-adipose cells, the breakdown of SC stomach tissue may help to explain why IR occurs in PCOS women who are slim. Additionally, it has been discovered through studies that women with PCOS who are slim experience hyperandrogenism, which is directly connected with intra-abdominal fat accumulation (Nestler & Jakubowicz, 1998)

Teenagers with PCOS who are thin have also been found to have hyperinsulinemia and IR . Insulin increases ovarian androgen hormone production while decreasing hepatic SHBG yield, resulting in the production of more and free androgens . In a nutshell, IR typically affects women of average weight and is associated with fat conveyance, which is crucial for youngsters who have the ailment. One of the main causes of PCOS in people is excessive androgen. According to several studies, there used to be no connection between the lipidomic profile and the hormone testosterone . Additionally, reports have shown that women with PCOS who do not have HA have low HDL levels . In order to grasp the HA enlargement in women with this illness, VAI truly makes it understandable . According to a report, the relationship between hormone levels and PCOS was looked at in the Pakistani population. In this particular analysis, healthy people underwent blood testing, including radioimmunoassays and immunological radiometric tests, to look into hormone alterations. In contrast to the healthy masses, a person with PCOS had high levels of LH, BMI, prolactin, and FSH as a result. There are a few key considerations that must be made in order to diagnose PCOS. These are the androgen levels, LH, and FSH. More LH causes androgen levels to increase, which essentially promotes PCOS progression (Liaqat *et al*., 2015). IGT is weak in about 35% of PCOS patients, and type 2 diabetes affects 7–10% of women . PCOS is associated with type 1, type 2, and gestational diabetes, among others . An expansion in the spread of IGT in women with PCOS was shown by a condensed research and meta-analysis of thirteen inspections that included 835 women with PCOS and 568 controls . In addition, a subgroup analysis of nine BMI-coordinated studies that included a sample of 347 women with PCOS and 319 controls was used to determine the expansion in IGT (Moran *et al.*, 2010). With the rise in obesity among women who have this illness, a modest increase in the prevalence of Type 2 diabetes was observed in some random scenarios. Additionally, a study under way revealed a connection between PCOS and diabetes in thin women . It must be highlighted that

type 2 diabetes severity cannot be predicted by age . An inactive lifestyle, including diet and exercise, can also contribute to PCOS. As women typically take on greater stress, which leads to sadness and anxiety in them, the metal state may also contribute to PCOS. Table 1 below discusses a few of them.

Table 1: Hormone imbalance with their noticeable effects.

S. No.	Types of hormones	Producing glands	Level	Effects
1.	Estrogen	Adrenal gland	Decreases	Less ovulation
2.	Androgen	Adrenal gland	Increases	Acne, more growth of hairs
3.	Insulin	Pancreas	Increases	Diabetes
4.	Progesterone	Adrenal gland	Decreases	Infertility problems
5.	FSH	Pituitary gland	Decreases	Pregnancy problems
6.	SHBG	Liver	Decreases	Obesity
7.	LH	Pituitary gland	Increases	Menopause

Biomarkers:

Polycystic ovarian syndrome is strongly associated with a poor cardiometabolic profile, more challenging medical diseases, abnormal glucose metabolism, pregnancy issues, acne, increased IR , obesity , and emphysema . However, a number of hormonal changes related to PCOS may take place; these specific changes may be referred to as "biomarkers." These abnormalities include an increase in IL-6, TNF-, HS-CRP, IL-1, triglycerides, LH, FSH, and 17-estradiol levels and a decrease in adiponectin, serum IL-10, progesterone, high-density lipoprotein, and so on.

There are a select few independent biomarkers as well, including haptoglobin chains 30c and 146a, C4 and C4R3c, and their derivatives. According to earlier studies, around 150 proteomic markers have been found in T cells, serum, omental, follicular, and ovary biopsies.However, only 11 of these were independently verified (Matharoo-Ball *et al*., 2007). There are still ongoing studies.

Treatment:

There are now relatively few medications available to cure polycystic ovarian syndrome, a condition that is particularly prevalent in females. Several techniques are listed below:

(a) **First-line therapy**

lifestyle modifications For instance, it has been demonstrated that decreasing body fat and combining daily exercise with a healthy diet will help PCOS sufferers and obese PCOS women conceive .Since some studies suggest that for hefty women it is fairly difficult to manage this without losing weight, changes in lifestyle or variations in it are very important for the smooth cycle of ovulation .Clomiphene citrate is the drug used to ensure a smooth ovulation cycle. No more than 100 mg of CC should be taken each day (Strowitzki & von Wolff, 2005)

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(b) **Second-line therapy**

Aromatase inhibitors, such as letrozole (Femara®), impede the conversion of testosterone and androstenedione to estradiol and estrone, which is necessary for the regulation of ovulation. Letrozole, in this way, balances out any negative complaints related to the higher frequency and promotes greater gonadotropin-releasing hormone production, which in turn boosts ovulatory follicle growth. Despite the fact that aromatase inhibitors have endometrium-damaging effects that are slightly less severe than those of CC (about 15%), the likelihood of pregnancy and the removal rate of the foetus are comparable to those of CC (about 15%). Grave concerns were raised following the findings of the (Biljan *et al.,* 2005) study, which revealed a higher risk of heart disease and skeleton defects in babies born with letrozole treatment during ovarian activation.

(c) **Third-line therapy**

Surveys have also demonstrated that using a GnRH stimulant results in higher rates of growing foetuses and lower rates of premature delivery when compared to CC treatment. In any case, IVF is frequently performed only on clomiphene-free individuals and those who are infertile for reasons other than anovulatory disorders (this could be due to the men factor).This discrepancy appears to be caused by the complexity of GnRH analogue therapy, which necessitates the administration of higher doses of gonadotropin-releasing hormone to achieve conception, increasing the number of follicles produced and increasing the risk of multiple pregnancies.

Pregnancy-related medications

Some medications may be able to help PCOS women have healthy pregnancies. A variety of reproductive medications containing synthetic hormones such as progesterone and oestrogen are also recommended by experts. These pills help regulate the menstrual cycle by lowering testosterone production. When a woman is taking anti-conception medication, getting pregnant can be extremely difficult . When menstruation first begins, clomiphene can be taken as an anti-estrogen tranquillizer. When the ovulation-improving effects of clomiphene are ineffective, a diabetic medication or prescription called metformin may be administered. Surprisingly, a medication containing FSH and LH is available if metformin and clomiphene stop working. Another medication that can be useful if other medications aren't helping is letrozole. An ultrasonography examination may be advised before prescribing any medicine if PCOS is suspected. The specific condition may be confirmed by ultrasonography. While high sex hormone levels, ovulation or oligomenorrhea, and especially pointlessness are some of the most common issues in PCOS women of reproductive age, HA and menstruation-related difficulties are some of the most common concerns in younger PCOS women.An abnormal ovulation is the most prevalent cause of infertility in this illness, with a prevalence of 68% (Pan *et al*., 2018)

Clomiphene

Frank Palopoli and his colleagues first discovered clomiphene in the 1950s, and it has since become the most widely recommended reproductive drug in the nation. Clomiphene is a non-steroidal, externally administered ovarian stimulant that acts as a direct oestrogen receptor modulator. Large numbers of ovulatory cycles brought on by clomiphene may enhance the likelihood of having twins. Mono-FSH is less likely to cause ovarian hyperstimulation than Clomiphene. Clomiphene does have the potential to connect with receptor-binding organs, such as the hypothalamus, pituitary, endometrial, ovarian, vaginal, and cervical ones, despite the possibility of an elevated risk of ovarian cancer as well as weight

gain. Preovulatory glycoprotein hormones surge as a result of a series of endocrine reactions brought on by clomiphene which leads to follicle breakup. Prior to the endocrine response to the duration of clomiphene medication, there is an increase in pituitary gonadotropin production, which essentially stimulates steroid synthesis and follicular growth, resulting in an increase in ovarian follicles and an increase in the amount of estradiol in the blood.

Mechanism of action

Although clomiphene has both estrogenic and anti-estrogenic properties, the precise mode of action is still unknown. In order to boost the development of ovarian follicles, the ovulation cycle, and the progression and capacity of the coprus luteum, clomiphene appears to stimulate the production of the gonadotrophic hormones (FSH) and apa. This helps to promote pregnancy. Clomiphene does not interfere with thyroid or pituitary-adrenal function, nor does it cause any detectable pregnancies or androgenic or antiandrogenic effects (Tomic & Tomic, 2012).GnRH antagonist techniques have been employed in IVF/ICSI in the past with a variety of patient populations and an anticipated high response rate. Individuals with polycystic ovarian syndrome, who are already more likely to develop OHSS after ovulation, are included in the final group. A predetermined set of scattered tests evaluating the application of GnRH modulation in PCOS-affected women undergoing IVF/ICSI is proposed. The rate of OHSS, medical conception rate, length of gonadotropin stimulation, artificial childbirth cycle proportion per medical childbirth, and multiple maternity percentages have all been used as alternative outcomes for the inquiry.

Conclusion

Women with PCOS are more likely to experience irregular periods, obesity, and pregnancy issues. The condition that affects women the most frequently by far is pregnancy, which is primarily brought on by ovulation problems. The women might not be able to create enough hormones for the development, maturation, or delivery of viable eggs. Given the current increase in the number of cases, the current comprehensive review would undoubtedly aid in better understanding and raising awareness of the issues surrounding this condition. This would undoubtedly inspire the scientific community to work a little harder to address this issue. The best therapies for it right now are calorie restriction, enough exercise, and allopathic medications (such as clomiphene citrate). There are benefits and drawbacks to each of these therapy options for polycystic kidney disease. Fitness methods and weight loss require time. Allopathic medicines cost a lot of money and can have unpleasant side effects. As a result, "let food become medication, and medication become eating," was said. In the future, it's possible to conduct studies on other herbal drug combinations and define the clinical importance of each of the composition's bioactive ingredients. Along with other therapy approaches, the pharmacological combination might be studied. Clinical trials may also be used to test the effectiveness of these kinds of techniques after their safety has been established.

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