The Link Between PCOS and Infertility: Exploring Science

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Abstract: The main cause in anovulatory infertility is PCOS, that affects 7–15% in women who are of reproductive age. Infertility impacts about 15% of couples and requires thorough evaluation, including history, physical, gynaecological, and endocrine assessments. The treatment of choice for PCOS-related infertility is clomiphene citrate. If it is ineffective, low-dose FSH stimulation is used to avoid problems such ovarian hyperstimulation and repeated pregnancies. Inhibitors of aromatase are new substitutes. Ovulation is improved by weight loss as well as insulin-sensitizing medications like metformin, though metformin is not advised unless metabolic issues are present. Myoinositol is a newer option under investigation. When medications fail, surgical methods such as laparoscopic ovarian drilling or transvaginal hydro laparoscopy are considered, particularly effective in lean women with high LH. IVF and in vitro maturation, which have outstanding success rates, are third-line choices. With current therapies, most women with PCOS-related infertility can achieve ovulation and pregnancy.

Keywords: PCOS, Hormone, Syndrome, Cyst, Infertility.

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Period of Study

The book chapter encompasses research conducted over a 19-year period, from 2004 to 2023, reflecting the evolving understanding and treatment approaches related to PCOS. In this few paper is from 1990.

I. INTRODUCTION

PCOS is a common endocrine and reproductive disorder that affects 5 to 15% of women during reproductive age, often those around the ages of 18 and 44. Stein-Leventhal Syndrome, that was initially described by Stein & Leventhal in 1935, is another name for it, as are multicystic ovaries and sclerocystic ovaries. The exact etiology of PCOS, that is characterized by a combination of genetic, environmental, and lifestyle factors, is still up for debate. The Rotterdam criteria, that define PCOS, include polycystic ovarian structure (ovarian volume >10 ml as well as >12 follicles per ovary), clinical as well as biochemical hyperandrogenism, and oligo/anovulation. A number of variables combine to develop PCOS, including elevated androgens, insulin resistance, stress, obesity, and a disturbed hormonal balance. frequently exhibit excess weight, infertility, hyperandrogenic symptoms (including hirsutism, acne, and seborrhea), and irregular menstruation. Around 70-80% of affected women experience anovulatory infertility. Diagnosis is frequently delayed due to late specialist referrals, often prompted only when infertility becomes evident. The purpose of this article is to give a summary of the available reproductive treatments for PCOS, with particular focus on

ovarian drilling—a lesser-used surgical approach with specific benefits in select cases.

II. TREATMENT

The most successful and first-line treatment for infertility is still non-pharmacologic. The benefits of gonadotropins, letrozole, and clomiphene citrate in treating PCOS-related infertility are already well established. This review will include two novel therapeutic approaches: myoinositol and ovarian drilling. Articles up until March 2021 are included in this review. Non-pharmacological interventions. A shift in lifestyle is the main treatment for women with PCOS. Smoking is always to be avoided, and exercise must always be encouraged. Obese or overweight women should reduce their weight. Numerous studies have shown that women who are obese or overweight may be enabled to resume regular ovulation and menstruation with only a 5-10% weight loss. Additionally, this weight loss intensifies the ovulation-inducing drugs' effects. Losing weight in obese women with PCOS raises their chance of getting pregnant in addition to the known metabolic benefits. When lifestyle modifications have been unsuccessful for more than a year and the BMI is greater than 35 kg/m2, bariatric surgery could Volume 10, Issue 5, May - 2025

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be taken into consideration. A meta-analysis found that testosterone levels significantly decreased in obese PCOS women who had bariatric surgery. which was linked to a 53% resolution of hirsutism and a 96% resolution of irregular menstruation. Nevertheless, there is not any solid proof yet that bariatric surgery increases the likelihood of conception in PCOS-afflicted women. Furthermore, it is important to pay attention to nutrient deficiencies, intestine confinement in Petersen space and the resulting surgical outcomes.

> Non-Pharmacological Measures

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> Metformin

Given the critical role which insulin resistance performs in PCOS, off-label use of the insulin sensitizer metformin has long been considered a first-line treatment. Numerous studies have suggested that metformin, either alone or in conjunction with clomiphene, might have enhanced ovulatory cycles in individuals with PCOS. However, pooled studies also showed that it had no impact on the live birth rate. Therefore, the current guidelines do not recommend using metformin to stimulate ovulation and limit its usage in insulin resistance accompanying PCOS and type 2 diabetes.

▶ Letrozole

Letrozole is a member of the aromatase inhibitor medication class. E2 levels decrease when aromatase inhibitors are used. This greatly reduces the likelihood of producing a large number of follicles. Among CC, this was one of letrozole's primary benefits. Another advantage is that letrozole does not interfere affecting endometrial estrogen receptors, therefore it does not affect cervical mucus as well as endometrial thickness. Letrozole may increase ovulation, according to Mejia and colleagues, however there is no proof that this treatment increases the likelihood of conception. For women with CC tolerance and failure who are not suffering from any reason of infertility, letrozole is still recommended as a second line of treatment.



Fig 1 Source(28)-Letrozole's mode of action. Letrozole stops testosterone from being converted to estrogen. Thus, estrogenic negative feedback is removed from the hypothalamic-pituitary axis, which raises pituitary FSH output and, in turn, improves ovulatory rates. Additionally, follicular sensitivity of FSH is improved by a rise in intraovarian androgens. 'Follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and estrogen receptor (ER)' Treatment has already been verified.

➢ Clomiphene Citrate

Clomiphene citrate (CC) remains the first-choice drug for ovulation induction in infertile women with PCOS. By inhibiting estrogen receptors of the brain and through a negative feedback mechanism, CC, an anti-estrogen therapy, promotes follicular growth. In order to recognize the ovulation time and prevent more than one pregnancy (11% risk), CC dosing must be followed by endocrine blood sample and ultrasound. On days 11 to 14, ultrasound examination is carried out as monitoring, along with measurements of endometrial thickness and follicular development.

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Fig-2 Source (20) Clomiphene citrate's mode of action. Because clomiphene citrate inhibits the hypothalamic estrogen receptors, the amplitude of the GnRH pulse increases, causing the release of more FSH (and LH) for a longer period of time and promoting the follicles' ultimate maturation. Follicle-stimulating hormone is referred to as FSH, gonadotropin-releasing hormone as GnRH, luteinizing hormone as LH, and estrogen receptor as ER.

Second Line Therapeutic Options: Gonadotropin Therapy A second-line option for treatment is gonadotropin therapy in conjunction with planned sex. Women with PCOS are currently advised to follow a low-dose step-up regimen to avoid ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Because of the high antral follicle count, women with PCOS are more prone to develop OHSS. The third line treatment option is in in vitro development and conception. More sophisticated treatments, primarily in vitro fertilization (IVF) as well as in more recent years, in vitro maturation (IVM), should be suggested when the second-line therapy alternatives have failed. Gonadotropins work in tandem with gonadotropin-releasing hormone agonists and antagonists in IVF procedures. OHSS and many pregnancies are complications of this method. Multiple luteinized cysts within the ovaries after ovulation cause the ovaries to enlarge and have higher vascular permeability, which causes the fluids to shift and create a third compartment. Vascular endothelial growth factors, such as estrogens, progesterone, and local cytokines, promote vascular hyperpermeability. Death, renal failure, and hypovolemia can result from the formation of a third space. OHSS is more common in women with PCOS because of the high number of antral follicles. Women with PCOS who get in vitro maturation (IVM) treatments may be able to avoid the high risk of OHSS and multiple pregnancies that come with IVF. In IVM,

gonadotrophin is stimulated for a brief period of time without the need of a trigger injection. Oocyte meiosis as well as maturation to metaphase II take place in vitro, and oocytes are extracted from smaller follicles compared to traditional IVF. This method offers a chance to reduce exposures to high E2 dosages in women with thrombophilia or breast cancer, which is especially tempting for PCOS women.

III. NEW TREATMENTS

> Myoinositol

One of the medicinal substitutes that has been studied recently is inositol. It serves as the initial treatment. Inositol comes in nine distinct stereoisomers. In both plant and animal tissues, myoinositol is abundantly distributed in nature. Second, D-chiro-inositol is a frequent isomer. Inositol is directly engaged in insulin cell signaling and can be generated from glucose in human cells. It functions as a second messenger inside cells to control hormones such as insulin, FSH, and TSH. Inositol has two functions with these stereoisomers: It enhances cell glucose transport by encouraging the translocation of glucose-transporter 4 (GLUT4) into the cell membrane; it also prevents adipose tissue from releasing free fatty acids. Adenosine triphosphate (ATP) is produced, glycogen is synthesized, and insulininduced androgen synthesis is regulated in the ovaries by D- Volume 10, Issue 5, May - 2025

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chiro-inositol's upregulation of the pyruvate dehydrogenase enzyme. D-chiro-inositol and myoinositol support the enzyme that results in glucose being converted to glycogen. Myoinositol regulates both FSH signaling and the ovaries' absorption of glucose, as well as the activating of glucose transporters and glucose utilization. It has been demonstrated that D-chiro-inositol administration lowers insulin resistance. Patients with PCOS have improved metabolic profiles thanks to inositol. Some studies suggest that a daily dose of 1 g Dchiro-inositol þ 400 mcg folic acid is necessary to reduce metabolic syndrome and increase the glycemia/insulin ratio. Regidor et al. examined the impact of a combination medicine for 2 and 3 months, which included two thousand myo-inositol and two hundred micrograms of folic acid daily. They proposed that women with PCOS who received myoinositol therapy had higher rates of conception and higherquality embryos. Consequently, myo-inositol at a dosage of 4000 mg daily is advised as an enhancement to IVF procedures for PCOS patients. Inositol has also been linked in studies to metabolic diseases and human reproduction, including ovulation. Inositol supplementation seemed to raise ovulation rates and menstrual cycle frequency, according to Pundir et al.'s review. No research, however, discovered a higher live birth rate.

> Ovarian Drilling

Another treatment option is laparoscopic or transvaginal ovarian drilling, also referred to as ovary diathermy or electrocoagulation. It serves as a backup course of care. In fact, this method can be suggested prior to gonadotrophin treatment and following 4–6 cycles of CC. The procedure known as "ovarian drilling" involves making punctures in the ovaries. The technique's goal is to make three to six punctures in the ovarian capsule using an electrosurgical probe.

Each point is 4 mm in diameter and 5–7 mm deep. The penetration takes 5 seconds. This method takes the place of cuneiform ovarian resection. Prior to the development of the ovarian drilling procedure, cuneiform resection was carried out, which might result in adherences and surgical problems. The very first transvaginal laparoscopy was carried out in 2001, while the first laparoscopic ovarian piercing was carried out in 1984. You can utilize both methods.

➤ Method.

Two extra trocars and a conventional endoscope are used for laparoscopic ovarian cautery. For four to five seconds, At an intensity of 40 W, the full length of the unipolar electrodes with needles is inserted into the ovary. The suggested procedure regarding ovarian drilling is the laparoscopic technique. Saline solution is used in the peritoneal cavity during transvaginal hydro laparoscopy. The endoscope can examine the whole pelvic cavity because of its 30-degree angle. Transvaginal laparoscopy (THL) is another method for doing salpingoscopy combined fallopian tube as well as fimbriae inspection. With roughly ten perforations for each ovary and a 10 mm depth of insertion, bilateral ovarian drilling had been carried out. Spinal anesthesia can be used to implement this procedure. As with any surgical procedure, there are risks associated with ovarian drilling, including the possibility of adhesion formation. The choice of procedure (laparoscopy versus THL) may have an effect on safety. Giampaolino et al. compared the benefits of laparoscopy and THL. The results showed that THL is faster, less likely to cause adhesions, as well as more easily tolerated by patients (less pain after surgery). These benefits may be due to the use of bipolar diathermy, the use of saline solution, a faster recovery period, and less bleeding because less ovarian manipulation is required than with a laparoscopy. For obese ladies, THL also has a simpler method. Lastly, Giampaolino et al. also imply that THL has a lower learning curve than laparoscopy.

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However, there is a 0.5% chance of rectum perforation with this method. If this occurs, antibiotics and cautious treatment are typically used to control it. A second-look laparoscopy will be used to confirm the peritoneal integrity. We still do not fully understand how ovarian drilling works. Ovarian drilling appears to decrease intraovarian androgen levels and hinder local androgen production, This decreases the follicular maturation-inhibiting effect. The peripheral conversion of androgen into estrogen and the advantage feedback for LH production are both diminished by lower testosterone levels. Both exogenous FSH stimulation and spontaneous recruitment of fresh follicles are allowed. This method helps with irregular periods, ovulation, pregnancy, hirsutism, and acne. Ovarian drilling doesn't need ultrasound monitoring and removes the risk of OHSS and multiple pregnancies. According to moderate-quality evidence presented in a Cochrane review in 2020, Laparoscopic ovarian drilling may result in fewer OHSS and probably reduces the number of multiple pregnancies. The literature varies on the effectiveness of ovarian drilling. There have been reports of ovulation as well as pregnancy rates of 30 -90% along with 13 to 80%, respectively. The approach is more effective when the LH concentration is high (>10UI/l), the infertile period is brief (35 kg/m2), insulin resistance is present, and the testosterone concentration is high. The outcomes may also be impacted by the technique used. Giampaolino et al. (2018) showed that ovulation happened in 82.9% of patients in the first six months after THL, which is equivalent to a 70% pregnancy rate. The long-term preservation of ovarian drilling's effects is another significant advantage, in addition to its effectiveness with regard to of pregnancy rate. In fact, research indicates that over 60% of patients will see symptom improvement or remission for as long as twenty years following the surgery. With the exception of lifestyle changes that are sustained over time, the other PCOS treatment methods do not provide this long-term efficacy. In a retrospective investigation conducted in 2020, Debras et al. shown that ovarian drilling has long-term effects and allows for spontaneous conception. A typical body mass index (BMI), The expected indicators for this effectiveness were age under 35, AFC below 50, and fewer then three years of infertility.

Clinical Features/ Sign & Symptoms

The complexity of this disorder does not appear in its name because it is associated with other conditions. The ovarian sac of PCOS patients is filled with several 8 mmsized cysts. There are over 12 cysts in the ovary.

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Approximately seventy percent of females with this condition are infertile. As was previously noted, PCOS is characterized by a rise in androgen, a hormone found in men, which leads to hirsutism and acne. Insulin resistance is the cause of type 2 diabetes with obesity. Infertility results from irregular menstrual cycles caused by this problem. Sleep apnea affects 20% of women on a regular basis. Depression and anxiety are common. A pie chart is used to illustrate the long-term PCOS condition.



Fig. 3. Source (8) PCOS is a chronicncondition.

> Diagnosis

This disease can be diagnosed using the Rotterdam criteria, which include the formation of cysts, an infrequent period, and an elevated testosterone level. The PCOS criteria for diagnosis are displayed in Table 1.

| - | | | |
|---|-------|-----------|---------------------------|
| | Table | e 1. PCOS | Diagnostic Standards [11] |

| NIH 1990 | Rotterdam 2003 | AE-PCOS society 2006 |
|--------------------------|----------------------|---|
| Long-lasting anovulation | Oligo or anovulation | Biochemical and clinical evidence of hyperandrogenism |
| Hyperandrogenism | Hyperandrogenism | Dysfunction ovaries |
| Empty Cell | Polycystic ovaries | Polycystic ovary morphology |

IV. ETIOLOGY OF PCOS

Both environmental and genetic variables may have contributed to the development of this condition. Unhealthy eating habits, lifestyle choices, and viral mediators all raise the risk of PCOS. In addition to its high level, insulin resistance disrupts ovarian function by increasing testosterone levels and causing anovulation. 'Prolactin, luteinizing hormone (LH), follicular stimulating hormone (FSH), and gonadotrophin-releasing hormone' levels are also impacted by PCOS. Genetic factors also have a role in the development of PCOS, alongside to environmental ones. The cause is SNPs, or candidate genes. According to databases, the pathophysiology of PCOS involves 241 gene variations. PCOS is caused by polymorphism as well as simply any nucleotide change that impairs a gene's transcriptional function. The genes encoding the 'androgen receptor, luteinizing hormone receptors, follicular stimulating hormone receptors, and leptin receptors' make up the majority of the relevant genes. The metabolic pathway is disrupted by a gene deficit, leading to ovarian dysfunction.

It has been discovered that some polymorphisms, including those involving 'StAR, FSHR, FTO, VDR, IR, IRS, and GnRHR', contribute to the development of PCOS. As insulin and androgen levels rise, so does the severity and progression of PCOS. Ovarian theca cells are impacted by hyperinsulinemia, which also raises testosterone levels. The hepatic production of SHBG as well as IGFBP-1 is decreased in this situation. Conversely, an increase in testosterone causes visceral adipose tissue (VAT) to produce free fatty acids (FFAs), which in turn leads to insulin resistance. Hyperandrogenism is described by a mechanism that links genetic propensity to PCOS.



Fig 4. How Insulin Resistance Affects and Disrupts the Activity of Ovarian Theca Cells (Source 18)



Fig 5 Source (19). LH and Testosterone are Elevated when there is a Pituitary Axis Malfunction. Insulin Resistance is another Consequence. Insulin Resistance and Elevated Testosterone levels Work together to Support the Anovulation Pathway.

V. CONCLUSION

Among the primary reasons for infertility, PCOS is a complicated reproductive, metabolic, as well as psychological condition with a wide range of clinical signs.

Before turning to pharmaceutical treatments for PCOSrelated infertility, lifestyle modifications should be the primary line of treatment. Ovulation induction is the next step, and letrozole is the best choice, followed by CC. Women who are not responding to oral ovulation induction treatment as a first line of treatment are treated with gonadotropins. ART or LOD can be utilized for women who have other infertility reasons or who do not conceive with ovulation induction medications.

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Fig 6 Suggested Treatment for Infertility Associated with Polycystic Ovarian Syndrome.

The best advised regimen for patients either IR or hyperinsulinemia is still to employ metformin as an adjuvant to IVF ± ICSI therapy and in conjunction with CC or gonadotropins.

The development of PCOS is linked to several putative genes in addition for natural variables. The metabolic pathway is altered by a gene abnormality, leading to ovarian malfunction and the progression of PCOS. The severity can only be reduced by adopting the appropriate precautions, such as decreasing weight, eating a healthy diet, and using prescription drugs.

Although bariatric surgery can help with PCOS-related comorbidities, it should currently be regarded as an experimental reproductive treatment. Vitamin D and inositol might be helpful, however further research is required before recommendations can be made.

The effectiveness of alternative therapy is not well established.

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