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Review Article

A Review on PCOS Causing Infertility

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ABSTRACT

Reproductive dysfunction is a common presentation for women with polycystic ovarian syndrome (PCOS). The pathophysiology of anovulation is difficult to pinpoint, however numerous potential pathways have been proposed. Ovarian activity may be disrupted, leading to aberrant folliculogenesis and steroidogenesis. Failure of dominance and the presence of several tiny follicles in the ovary that are arrested but capable of steroidogenesis are characteristics of folliculogenesis in anovulatory women with PCOS. Disordered paracrine activity and abnormalities in gonadotrophin and insulin secretion have been found. Miscarriages following both spontaneous and artificial ovulation are more common in women with PCOS. Hyperandrogenemia, hyperinsulinemia, and hypersecretion of LH have all been studied as potential causes of PCOS. These elements are probably connected, and when combined, they could cause disorganised. These elements are probably connected, and when combined, they may cause abnormal endometrial and ovarian function. Reproductive failure has been attributed to a number of additional potential disorders. These include obesity, endothelial dysfunction, and a decrease in plasminogen activator inhibitor activity. Therapy should ideally target the underlying diseases, but current data are insufficient, and further research is necessary before recommendations for treatment are genuinely grounded in a pathophysiology understanding Various diagnostic and contemporary approaches were also enclosed in this review.

INTRODUCTION

Stein Leventhal Syndrome is another name for PCOS (Polycystic Ovary Syndrome). Clusters of tiny, pearl-sized cysts in the ovaries are a common side effect of PCOD. Immature eggs are contained in fluid-filled cysts. Both environmental and genetic variables could be involved in this illness. In addition to causing changes in physical appearance and irregular menstrual cycles, PCOD increases the risk of diabetes, heart attacks, obesity, mood disorders, endometrial cancer, and sleep apnoea if treatment is delayed. Women with

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PCOD typically fall within the 14–44 age range. Although there is no known treatment for this illness, research has shown that hormones, medications, a good diet, and exercise.To be polycystic is to have multiple cysts. A complicated illness characterised by both clinical or biochemical hyperandrogenism and chronic oligoanovulation or oligomenorrhea is known as polycystic ovarian disease. (1) In the pubertal age group, it is the most frequent cause of irregular uterine bleeding. An estimated 20% of Indian women are thought to have PCOD.(2) Unawareness and ignorance among young women can contribute significantly to the rise of PCOS cases in our world. Reproductive failure may result from undiagnosed PCOD. 5% to 10% of women who are between the ages of 15 and 44 who are of reproductive age have PCOS. When women seek medical attention for infertility and discover they have PCOS, this is typically when they are in their second or third decade of life. The age range that is most impacted, according to the report, is 15 to 25. Research shows that one in five Indian women and one in four women in East India have PCOS.(3) A diagnosis made using what are known as the Rotterdam criteria. This comprises three elements, two of which are necessary for a provisional diagnosis of PCOD, namely: 1) Hyperandrogenism, which is the presence of symptoms associated with elevated androgenic hormones, 2) Hyperandrogenemia, which is the presence of elevated androgen levels in the blood with or without symptoms.(4) Menstrual abnormalities, namely secondary amenorrhoea and oligomennorrhea, are of special 3)The USG shows a polycystic ovary >/= 10 cc >/= 12 follicles in the ovary. polycystic ovarian syndrome (PCOS) can have a major effect on fertility. Because of the hormonal abnormalities it creates, especially those linked to insulin resistance and elevated androgen, it is one of the most common reasons of female infertility**(5)**. The characteristic of infertility is the inability to produce a clinical pregnancy after 12 months of regular, unprotected sexual activity. Globally, it is estimated that 8–12% of couples in the reproductive age range are impacted. Men are reported to be solely responsible for 20–30% of infertility cases, despite making up 50% of all cases. Secondary infertility is the most common form of infertility in women globally and is often caused by infections and diseases like PCOS the reproductive system . (4) Seven to fifteen percent of women in their reproductive years suffer from PCOS, a prevalent gyne-endocrine condition and the leading cause of infertility. (6)When there are no other male or female reasons of infertility, clomiphene citrate is still the first line of treatment for infertility in women with PCOS. In the absence of a metabolic abnormality and a novel medication, such as myoinositol, it is not advised to use metformin exclusively for infertility. When medical treatment fails, surgical methods to increase ovulation and pregnancy rate may be used. Infertility is increasingly being treated with ovarian drilling via laparoscopy or transvaginal hydrolaparoscopy.**(7)**PCOS is the first cause of female infertility but the definite diagnosis should be given after exclusion of other etiologies of infertility such as other endocrine disorders (thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, premature ovarian insufficiency, …), anatomical dysfunctions (endometriosis, pelvic inflammatory diseases, …) or iatrogenic causes (surgery, chemotherapy, radiations, …)(8)

Symptoms

Additional symptoms include:

- Menstrual irregularities: oligomenorrhea, amenorrhoea, and prolonged erratic menstrual bleeding are common menstrual disturbances in PCOS

- Weight gain: Obesity, weight gain, or difficulty losing weight, especially around the waist.
- Fatigue: Up to 70% of women with PCOS report increased fatigue and low energy, along with related problems like poor sleep.
- Hirsutism: Extreme hair growth can occur on the face, arms, back, chest, thumbs, toes, and abdomen, and is linked to PCOS due to hormonal changes. Thinning hair on the head: The high level of androgens causes hair loss or thinning of the scalp.
- Infertility: Ovulation does not occur as a result of the absence of a dominant follicle Acne: Hormonal fluctuations related to androgens can cause acne. PCOS is also linked to dark areas of the skin. When a woman presents with acne, some specialists advise asking her about her menstrual history and checking her for additional hyperandrogenism symptoms Mood swings: Anxiety and depression are prevalent symptoms Pelvic discomfort: During periods, severe bleeding may be accompanied by pelvic pain. A headache Sleep issues: Women with PCOS frequently complain of issues like poor sleep or sleeplessness. Sleep apnoea, a sleep problem, has been connected to PCOS. (9)

Etiological Factors

Hypersecretions of LH

During the follicular phase of the cycle, PCOS is linked to tonic hypersecretion of LH, which may have a negative impact on fertility and the result of pregnancy. LH hypersecretion may result from anomalies in the amplitude and frequency of the LH pulse or from high oestrogen levels associated with PCOS.Furthermore, hyperinsulinemia may affect the gonadotroph and cause an increase in the release of LH.Women who planned to get pregnant and had regular menstrual cycles were the subjects of a prospective study that examined follicular-phase LH concentrations and pregnancy outcomes. Higher LH levels were associated with a lower chance of conception (67%) and a higher chance of miscarriage (65%) compared to women with normal LH levels, of whom 88% became pregnant and 12% experienced an early pregnancy loss. The authors came to the conclusion that continuously elevated LH levels decreased conception and embryo survival, and that hypersecretion of LH led to reproductive dysfunction. Further research on PCOS-afflicted women has shown that individuals with elevated follicular-phase LH concentrations have lower rates of ovulation and conception as well as greater rates of pregnancy loss. Watson et al examined multiparous controls and women who experienced repeated early pregnancy loss. In contrast to just one control, they discovered that 81% of women with recurrent loss had polycystic ovaries on ultrasound examination; this number is consistent with the documented prevalence of polycystic ovaries in the general population. Additionally, they examined serum and urine levels of LH, finding that 75% of patients who experienced an early miscarriage had higher urinary LH concentrations. Repeated measurements are likely to be more informative because single measurements of LH may not show intermittently elevated levels due to the pulsatile nature of LH secretion. The daily urine measurements acquired in Watson's study are probably more instructive because neither Watson et al nor Sagle and co-authors were able to show elevated LH levels when only one serum sample was analyzed. There are several potential explanations for why excessive LH secretion could lead to pregnancy loss. By inhibiting the oocyte maturation inhibitor, inappropriate LH secretion during the follicular stage may result in premature oocyte maturation. Increased LH-induced hyperandrogenism may affect ovarian folliculogenesis, leading to aberrant granulosa cell

activity and follicular atresia. Lastly, the endometrium may be impacted by the aberrant endocrine environment, and endometrial non-receptivity may be the secondary cause of miscarriage. Numerous studies on fertility therapy have provided additional evidence that elevated LH may play a role in miscarriage by showing that women with elevated LH levels were more likely to experience an early pregnancy loss if they became pregnant and were less likely to respond well to clomiphene citrate treatment. It seemed sense to implement a treatment plan that suppressed elevated LH levels, preventing the early stages of pregnancy from being exposed to the potential consequences of hypersecretion.**(10)**

Hyperandrogenaemia

PCOS is frequently associated with hyperandrogenism. Due to a decrease in sex hormone binding globulin (SHBG) levels and an increase in free circulating bioactive androgens, obesity intensifies the effects of increased androgens.It has been observed that early pregnancy serum progesterone and androgen levels can predict the outcome of the pregnancy, and patients who later miscarried had higher free testosterone ratios. When compared to women with ongoing pregnancies, PCOS patients who experienced repeated miscarriages had greater levels of circulating androgens. Gonadotrophin levels in their study were normal, but as only one measurement was made, this may not accurately represent the endocrinopathy. It has been demonstrated that women who experience repeated miscarriages, whether or whether they have PCOS, have greater testosterone levels than healthy, fertile volunteers. According to androgens may impair endometrial function by impeding the proper growth of the endometrium in both the luteal and follicular phases. Also verified that androgens have an inhibitory influence on the development and activity of endometrial cells. Granulosa cells may also convert androgens to oestrogens more often, which raises oestrone and oestradiol concentrations and, in turn, raises LH levels by providing a positive feedback loop to the pituitary. Consequently, androgens may have a negative impact on ovarian, endometrial, or pituitary fertility and pregnancy outcomes.**(11)**

Hperinsulinaemia

Ovarian androgen production rises as a result of hyperinsulinemia and hypersecretion of LH, which affect the androgen economy. Insulin resistance is more common in obese women, however it can equally afflict thin people. According to reports, a higher prevalence of recurrent pregnancy loss is linked to insulin resistance, and improving insulin sensitivity and reducing intra-abdominal fat by dietary and lifestyle changes can raise one's capacity for reproduction. Obesity alone may have an effect on reproductive function, or hyperinsulinemia may influence the outcome of pregnancy by interacting with LH and androgen production. PCOS patients with hyperinsulinemia have been treated with metformin, a biguanide that increases insulin sensitivity. The development of regular ovulatory cycles and spontaneous conception can correct many of the metabolic problems. There are numerous published research on the impact of metformin on early pregnancy loss in PCOS individuals. Confounding factors need to be considered before management decisions are made because obese women with insulin resistance are also more likely to have poor pregnancy outcomes, both in PCOS and in healthy women.The initial line of treatment for women with PCOS should focus on weight loss and lifestyle changes because these are significant contributors in decreasing insulin resistance.**(12)**

Pathogenesis

Abnormal steroidogenesis and impaired folliculogenesis are two interrelated characteristics of ovarian function in infertile women with PCOS. Disorders in one are caused by abnormalities in the other, and it has been challenging to pinpoint the

initial anomaly.

On ultrasound examination, the polycystic ovary can be recognised by its morphological characteristics, which include hyperechogenic stromal expansion and several tiny follicles that are either dispersed throughout the stroma or grouped around its periphery and range in diameter from 2 to 8 mm. Histological investigations have shown that whereas polycystic ovaries have a much higher number of primary and secondary follicles than normal ovaries, the number of primordial follicles is the same. Despite what was initially taught, these little follicles are arrested rather than atretic. They are capable of reacting to gonadotrophic stimulation and are viable and actively engaged in the steroidogenesis process. This brings up the main issues of how the follicles avoid the natural atresia process and why dominance fails.**(13)**

Normal folliculogenesis and steroidogenesis

The several phases that a primordial follicle goes through to mature into a preovulatory Graafian follicle are together referred to as follicular development. Primordial follicles develop into primary and subsequently secondary follicles during the preantral development phase. The mature secondary follicle is distinguished by granulosa cells that have receptors for follicle stimulating hormone (FSH), oestrogen, and androgens, as well as a theca layer that has luteinizing hormone (LH) receptors and the ability to produce steroids.

During the ensuing growth phase, a cohort of secondary follicles is converted into small antral follicles of 2–5 mm diameter. (14) This phase, which lasts for three ovarian cycles, calls for modest amounts of FSH. In the late luteal phase, a number of follicles are selected from this cohort. As a result of the follicles' increased production of oestrogen in the granulosa cells due to the influence of growing FSH levels, exponential follicular expansion ensues.When LH is stimulated, the theca cells produce the androgenic precursors required for the synthesis of oestrogen. Increased levels of intraovarian oestrogen and inhibin cause the granulosa cells of the developing follicle to upregulate FSH receptors, which in turn causes a negative feedback loop on FSH secretion and, via paracrine processes, a rise in the generation of thecal androgen. This leads to the eventual selection of a single dominant follicle that will ovulate and an increase in intrafollicular oestrogen production in spite of declining FSH levels.(15) The granulosa cells develop LH receptors once the developing follicle reaches a diameter of 9–10 mm, and subsequent steroidogenesis and oocyte maturation are dependent on LH. Progesterone, androgens, LH, and insulin can all promote or enhance the expression of the LH receptor on granulosa cells, even though FSH and oestrogen are the primary physiological stimuli for this process.14 The mature granulosa cells' acquisition of the LH receptor seems to "switch" the follicle from proliferation to differentiation, a process linked to early progesterone synthesis, a rise in steroidogenesis, a halt in granulosa cell development, and subsequent luteinisation. Progesterone causes the midcycle LH surge (via positive feedback to the pituitary) in conjunction with the elevated oestrogen levels, leading to ovulation. Atresia eliminates recruited but unsuccessfully dominant follicles, which are characterised by decreased oestrogen production, an elevated intrafollicular androgen/oestrogen ratio, and a higher reliance on continuous FSH stimulation. Growth factors, cytokines, and other ovarian peptides are involved in a number of paracrine and autocrine processes that affect and modify physiological pathways.(16)

Folliculogenesis in PCOS -In PCOS, the early follicular development phase is normal up to an average follicular diameter of 5 mm. Follicle

growth is therefore prematurely stopped as a result of the disruption of follicular maturation.

Decreased FSH

The failure of follicular formation in PCOS has been attributed in part to a relative FSH shortage. This could be the consequence of hypothalamic-pituitary feedback brought on by elevated ovarian steroid concentrations or secondary to increased inhibin synthesis.It is yet unknown how inhibin contributes to the pathophysiology of anovulation in PCOS.

Ovarian steroidogenesis and pituitary FSH secretion are known to be modulated by inhibitors, which are dimeric glyoproteins made in the ovary. FSH secretion is preferentially inhibited by Inhibin-B. Research assessing the levels of inhibin-B in the blood or follicular fluid of PCOS-afflicted women has found both elevated and normal levels.(17)

Maturation arrest by LH-An early reaction to LH stimulation by the granulosa cells of tiny antral follicles. This could result from either an increase in the LH stimulus caused by hyperinsulinemia and/or hyperandrogenemia, or by anomalies in LH secretion. Oestradiol and progesterone are produced by human granulosa cells from both normal and polycystic ovaries in response to insulin stimulation. Additionally, granulosa cells from tiny antral follicles that were preincubated with insulin showed a marked increase in cellular responsiveness to subsequent LH stimulation. Granulosa cells in ovulatory women with either normal or polycystic ovaries reactedonce a follicle's diameter had grown to 9.5–10 mm. In contrast, granulosa cells generated from follicles as tiny as 4 mm demonstrated LH responsiveness in anovulatory women with polycystic ovaries. Based on the in vitro results, the authors hypothesised that hyperinsulinemia causes early pregnancy loss and premature infertility in PCOS 759 maturation of granulosa cells in vivo in anovulatory women with PCOS. These investigations also highlight the gonadotrophic qualities of insulin.Because it inhibits granulosa cell growth and aromatase activity, boosts progesterone synthesis, and ultimately causes a halt to normal follicular development and failure of dominance, this early response is harmful to continued follicular maturation. In conclusion, these findings suggest that insulin is essential for follicle growth arrest. Thus, it is not unexpected that anovulation is more closely linked to hyperinsulinemia than to any of the other biochemical or clinical features of PCOS.(18)

Growth factors' function in follicle growth arrest-Growth factors' like paracrine regulation of ovarian function has been identified and described in recent years. A growth factor produced from oocytes, growth differentiation factor 9 (GDF-9) is expressed specifically in developing oocytes.GDF-9 loss prevented follicular development past the primary, one-layer follicle stage in transgenic mice, demonstrating its crucial function in folliculogenesis. The total absence of follicular atresia was maybe even more remarkable. The scientists came to the conclusion that a lack of GDF-9 caused folliculogenesis to be stopped before the granulosa cells were capable of starting apoptosis. An additional rodent investigation demonstrated GDF-9's capacity to inhibit granulosa cell expression of the LH receptor.The expression of GDF-9 mRNA was shown to be lower in developing oocytes in polycystic and PCOS ovaries compared to normal human ovaries and polycystic ovaries. The authors postulated that the pathophysiology of aberrant follicular development in this group of women may be influenced by aberrant expression of GDF-9. The aberrant ovarian function of women with PCOS is also linked to epidermal growth factor (EGF) and its analogue, transforming growth factor (TGFa), which acts via the EGF receptor. Normal follicle maturation seems to depend on physiological levels of EGF and TGFa, and

changes in local expression may be harmful.(19). Research on humans and rats has shown that EGF and TGFa significantly reduce the amount of oestrogen produced in granulosa cells when FSH is present. Both EGF and TGFa caused the granulosa cells of preantral follicles in rodents to undergo follicular maturation arrest and to decrease the synthesis of oestrogen. EGF affected human granulosa cells that were taken from polycystic and unstimulated normal ovaries. The mean peak oestradiol levels of polycystic ovarian granulosa cells were greater than those of normal ovarian granulose cells in response to FSH stimulation. This result bolsters the idea that PCOS's stopped follicles are viable. (20) Both groups' synthesis of FSH-induced oestrogen was suppressed when EGF was added to the cell culture. It has been demonstrated that granulosa cells produced from ovulatory polycystic ovaries and from ovaries in women with PCOS express noticeably more EGF receptors than granulosa cells obtained from normal ovaries. Ovulatory. and anovulatory polycystic ovaries may have higher local responses to TGFa due to their enhanced expression of EGF receptors, even if TGFa concentrations do not seem to differ between normal ovaries.An elevated local response to TGFa may be the consequence of EGF receptor expression. It has also been demonstrated that the cytokine tumour necrosis factor a (TNFa) regulates ovarian function locally by influencing follicle development, steroidogenesis, and apoptosis. Poor-quality oocytes in women receiving assisted reproductive procedures have been linked to changes in TNFa concentrations in follicular fluid.(21)

Reduction in apoptosis-Most human follicles are eliminated by atresia rather than reaching a stage of ultimate maturity. Endocrine, paracrine, and autocrine variables all have a significant impact on the closely controlled process of follicle apoptosis.It seems to start in the granulosa cells and could be brought on by any change between proapoptotic (death) and antiapoptotic (survival) factors, the latter of which most likely includes an elevated androgen/oestrogen ratio.Granulosa cell death has been suggested to be stimulated by the p53 tumour suppressor gene and the Fas ligand. The p53 target genes and growth factors that either promote (bax, basic fibroblast growth factor) or inhibit (mdm2, bcl 2, TGFa) apoptosis are responsible for this process. Research using transgenic mice has demonstrated that both TGFa and BCL 2 overexpression lead to reduced apoptosis and enhanced folliculogenesis.38. The ovaries of transgenic mice lacking GDF-9 have already been shown to exhibit no apoptosis.The polycystic ovary's increased number of viable primary and secondary follicles suggests that the apoptotic process is lessened. The precise mechanism by which PCOS may cause aberrant apoptosis, or even vice versa, is yet unknown, despite the allure of hypothesising that aberrant growth factor expression contributes to the dysregulation.(22)

Unusual steroid production in polycystic ovaries-Ovarian steroid production problems are closely associated with aberrant folliculogenesis. While the hallmark biochemical and clinical characteristic of PCOS is hyperandrogenism, aberrant synthesis of progesterone and oestrogen may also be present.(23)

The role of theca cells-Because serine phosphorylation regulates the activity of P450c17, the primary regulating enzyme of androgen production, the theca cells of women with ovulatory and anovulatory PCOS hypersecrete androgens. The insulin receptor is the target of excessive serine phosphorylation, which results in a downstream malfunction of insulin receptor signalling and aberrant insulin action on glucose metabolism. This is a genetic flaw, and it has been hypothesised that the lady with PCOS may have both insulin resistance and hyperandrogenism due

to this one mutation. The primary regulating enzyme of androgen production, P450c17, is activated more in the theca cells of women with ovulatory and anovulatory PCOS. This activity is influenced by serine phosphorylation. When the insulin receptor is the target of excessive serine phosphorylation, insulin receptor signalling is defective downstream, which results in aberrant insulin action on glucose metabolism. It has been suggested that this one anomaly could account for the lady with PCOS's insulin resistance and hyperandrogenism. It is a hereditary flaw. Both ovulatory and anovulatory women with polycystic ovaries exhibit hyperandrogenism, suggesting that aberrant ovarian function rather than hypersecretion of LH, which is present in many (but not all) anovulatory PCOS women, is the underlying cause.(24)

Function of granulosa cells-Precursors for granulosa cells to produce oestrogen are more readily available as a result of the androgen drive in the theca cells. Despite this, ovulatory women with PCOS do not have changed oestrogen secretion, and LH-induced aromatase activity does not start until the follicle has grown to a diameter of 9–10 mm. On the other hand, women with PCOS and anovulation exhibit increased aromatase activity in their granulosa cells in response to FSH and LH stimulation, which leads to higher synthesis of progesterone and oestrogen. This rise in aromatase activity is probably due to insulin, which both independently and in concert with gonadotrophins promotes the generation of progesterone and oestradiol. The generation of LH is tonically affected by the elevated levels of circulating oestrogen. The cycles of aberrant folliculogenesis, aberrant steroidogenesis, and aberrant gonadotrophin secretion are thus sustained by providing negative feedback to FSH secret(25)

Pathophysiology Of Pregnancy Loss-About 15% of all clinically recognised pregnancies end in early pregnancy loss. However, if the additional 15% or more foetuses lost prior to a clinical diagnosis are taken into account, the actual miscarriage rate is far greater. Approximately 1% of women will experience recurrent pregnancy loss, which is defined as three or more consecutive spontaneous losses, even though 30 to 50% of conceptions result in miscarriage. There are numerous potential underlying causes for recurrent miscarriages, but in around half of the cases, no clear explanation has been found. Both spontaneous and aided conceptions have been found to have chromosomal abnormalities, which are a prevalent cause of early development failure.(26**)** Additional causes include PCOS, other prothrombotic conditions, anatomical anomalies, and the antiphospholipid antibody syndrome. Other possible issues include endocrine disorders, environmental variables, and infections, for which there is less strong evidence of a causative role in pregnancy loss, in addition to these causes, which have been pretty well identified. Women who experience recurrent miscarriages seem to have a high frequency of PCOS. According to one study, 82% of women who presented with recurrent miscarriages had polycystic ovaries. Elevated blood LH levels have been linked to miscarriage in a number of studies. Although not always successful, therapeutic approaches were developed to address this anomaly. Subsequent research has revealed additional potential contributing mechanisms, and it appears likely that a number of interconnected factors, including hyperandrogenism, insulin resistance, obesity, aberrant folliculogenesis, and infertility treatment itself, are responsible for the underlying pathogenesis of early pregnancy loss in PCOS.**(27)**

Diagnosis-A comprehensive history and physical examination should be the first steps in the diagnostic process. Clinicians should pay close attention to the patient's menstrual history,

cutaneous features (e.g., terminal hair, acne, alopecia, acanthosis nigricans, skin tags), and any weight fluctuations and how they affect PCOS symptoms.Enquiries concerning prevalent PCOS comorbidities should also be made of patients. (28)Although recommendations vary throughout guidelines, the Endocrine Society recommends that practitioners use the 2003 Rotterdam criteria to diagnose PCOS. The Rotterdam criteria state that at least two of the three following findings must be present for a diagnosis: polycystic ovaries, ovulatory dysfunction, and hyperandrogenism.Without the use of ultrasonography or other imaging, the diagnosis may typically be made with a thorough history, physical examination, and simple laboratory tests. Excessive acne, androgenic alopecia, or hirsutism (terminal hair in a male-pattern distribution) are clinical indicators of hyperandrogenism. Elevated serum levels of total, bioavailable, or free testosterone or dehydroepiandrosterone sulphate are chemical indicators of hyperandrogenism. In the rare event that an androgen-secreting tumour is suspected (for example, when a patient exhibits significant virilisation or sudden development of PCOS symptoms), measuring testosterone levels can be useful. Ovulatory dysfunction includes amenorrhoea (absence of menstruation for 6 to 12 months after a cyclic pattern has been established) and oligomenorrhea (cycles more than 35 days apart but less than 6 months apart).**(29)**

Ultrasonography-An ovary with 12 or more follicles (or 25 or more follicles using current ultrasound technology) with a diameter of 2 to 9 mm, or one with an ultrasonography volume of more than 10 mL, is considered polycystic. Polycystic ovaries can be diagnosed with a single ovary that satisfies one or both of these criteria. Nevertheless, unless imaging is required to rule out a tumour or the patient satisfies only one of the other Rotterdam criteria for PCOS, ovarian ultrasonography is not required., Up to 62% of patients with regular ovulation have polycystic ovaries that fit the aforementioned criteria; the frequency decreases with patient age. **(30)**Further investigation of suspected PCOS aims to identify and treat long-term metabolic problems as well as rule out other curable illnesses that may mimic PCOS. Delaying the workup for PCOS in adolescents until they have been oligomenorrheic for at least two years makes sense because anovulation is frequent after menarche. It has been proposed that before an adolescent is diagnosed with PCOS, she should fulfil all three of the Rotterdam criteria .Both endocrinologic and neoplastic aetiologies are included in the wide differential diagnosis of PCOS. An algorithm for the workup of certain presentations is shown in Figure **(31)**Both endocrinologic and neoplastic aetiologies are included in the wide differential diagnosis of PCOS. An algorithm for the workup of certain presentations is shown in Figure . The Endocrine Society advises ruling out pregnancy, thyroid issues, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia in any woman with suspected PCOS.. Conditions like primary ovarian insufficiency and hypothalamic amenorrhoea should also be ruled out based on presentation. An androgen-secreting tumour should be ruled out in women who exhibit considerable virilisation, such as clitoromegaly or deepening of voice, or who have symptoms that appear quickly. Lastly, patients with physical signs that point to either acromegaly or Cushing disease should be ruled out. If the patient has no suggestive physical findings, there is no need to order laboratory tests for these illnesses.**(32)**Measurements of LH and follicle-stimulating hormone (FSH) levels to calculate a serum ratio of LH/FSH are additional tests that might be useful but are not required for diagnosis. Although PCOS is typically indicated by a ratio greater than 2, there are no precise cutoff values due to the wide variety of tests employed.For the

purpose of ruling out ovarian failure, the FSH level is more useful.**(33)**

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. Ovarian drilling and myo-inositol are novel therapeutic **(34)**

Non Pharmacological Interventions

The primary line of treatment for women with PCOS is a change in lifestyle. Exercise should always be promoted and smoking should always be avoided. It is advised that women who are overweight or obese lose weight. According to several studies, women who are overweight or obese may be able to resume regular menstruation and ovulation with just a 5–10% weight decrease. Additionally, this weight loss intensifies the ovulation-inducing drugs' effects. In addition to the established metabolic advantages, weight loss in obese women with PCOS increases the likelihood of becoming pregnant overall. When lifestyle modifications have been unsuccessful for more than a year and the BMI is greater than 35 kg/m2, bariatric surgery may be considered . According to a meta-analysis, when obese women with PCOS underwent bariatric surgery, their testosterone levels significantly decreased, which was linked to a 53% resolution of hirsutism and a 96% resolution of irregular menstruation . Nevertheless, there isn't any solid proof yet that bariatric surgery increases the likelihood of conception in PCOS-afflicted women. Furthermore, it's important to pay attention to nutrient deficiencies, intestinal confinement in Petersen space, and surgical consequences.**(35)**

Metformin

Off-label usage of metformin, an insulin sensitiser, has long been regarded as a first-line treatment for PCOS because of the crucial role that insulin resistance plays in the condition. According to a number of studies, women with PCOS who used metformin, either by alone or in combination with clomiphene, experienced longer ovulatory periods . Pooled investigations, however, also revealed that it has no effect on the live birth rate. Therefore, the current guidelines restrict the use of metformin to insulin resistance in PCOS and type 2 diabetes and do not suggest its use for ovulation induction. **(36)**

1ST Line Treatment

Citrate of clomiphene

For women with PCOS who are infertile, clomiphene citrate (CC) is still the first-choice medication for ovulation induction . By blocking the hypothalamic oestrogen receptors, CC is an anti-estrogen treatment that stimulates follicular development through a negative feedback mechanism . To understand the day of ovulation and avoid multiple pregnancies (11 percent risk), CC administration must be observed (by ultrasound and endocrine blood sample) . On days 11 to 14, ultrasound examination is carried out as monitoring, and measurements of endometrial thickness and follicular growth are also made.**(37)**

Letrozole

Letrozole belongs to the class of drugs known as aromatase inhibitors. Inhibitors of aromatase cause E2 levels to drop. This significantly lowers the chance of developing numerous follicles. Among CC, this is one of letrozole's primary benefits. Another benefit is that letrozole has no negative effects on cervical mucus or endometrial thickness since it does not interfere with endometrial oestrogen receptors . Letrozole may increase ovulationFor women with CC resistance or failure who do not have another infertility cause, letrozole is a second-line therapy. **(38)**

2nd Line Treatment

Gonadotropin therapy

Gonadotropin therapy combined with scheduled sexual activity is a second-line treatment option. A low-dose step-up regimen is currently

recommended for women with PCOS in order to prevent multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Women with PCOS are more likely to develop OHSS due to their high antral follicle count.**(39)**

3rd Line Treatment

IVF and IVM

More sophisticated treatments, primarily in vitro fertilisation (IVF) and, more recently, in vitro maturation (IVM), should be suggested after 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. Numerous luteinized cysts form inside the ovaries following ovulation, resulting in bigger ovaries with greater vascularpermeability, which causes the fluids to shift, creating a third space.**(40)** Vascular endothelial growth factors, such as oestrogens, progesterone, and local cytokines, promote vascular hyperpermeability. Death, renal failure, and hypovolemia can result from the formation of a third space. The large number of antral follicles in women with PCOS makes them more likely to develop OHSS. The in vitro maturation (IVM) treatment may help women with PCOS avoid the significant risk of OHSS and multiple pregnancies associated with IVF. In IVM, gonadotrophin is stimulated for a brief period of time without a trigger injection. Compared to traditional IVF, oocytes are extracted from smaller follicles. Meiosis and metaphase II maturation of oocytes take place in vitro. This method is especially appealing to women with PCOS and offers a chance to reduce exposure to high E2 dosages in women who have thrombophilia or breast cancer.**(41)**

Contemporary Treatments

Myoinositol

One of the medicinal substitutes that has lately been studied is inositol .It serves as the initial course of therapy. Inositol has nine distinct stereoisomers. Plant and animal tissues contain myoinositol in large quantities. A second prevalent isomer is D-chiro-inositol. Human cells can manufacture inositol from glucose, and it plays a direct role in the cellular signalling of insulin . It controls hormones like insulin, FSH, and TSH by functioning as an intracellular second messenger. With these stereoisomers, inositol has two distinct functions: first, it promotes the translocation of glucose-transporter 4 (GLUT4) to the cell membrane, which improves cell glucose transportation; second, it inhibits the release of free fatty acids from adipose tissue.**(42)**The pyruvate dehydrogenase enzyme is upregulated by D-chiro-inositol, which results in the synthesis of adenosine triphosphate (ATP), glycogen, and, in the ovaries, insulin-induced androgen synthesis. Myoinositol and D-chiro-inositol facilitate the enzyme that causes glucose to be converted to glycogen. **(43)**In addition to controlling glucose uptake and FSH signalling in the ovaries, myoinositol also modifies the activation of glucose utilisation and glucose transporters.It has been demonstrated that administering D-chiro-inositol lowers insulin resistance. PCOS patients' metabolic profiles are improved by inositol. According to certain research, in order to lower metabolic syndrome and raise the glycemia/insulin ratio, a daily dose of 400 mcg folic acid plus 1 g D-chiro-inositol is required . For two and three months, Regidor et al. investigated the effects of a combined medication consisting of two × 2000 mg myo-inositol and two × 200 mcg folic acid daily. They proposed that myo-inositol therapy improved the quality of the embryos and the rate of fertilisation in women with PCOS. Consequently, it is advised that people with PCOS take 4000 mg of myo-inositol daily as an enhancement to IVF procedures. **(44)**

Drilling in ovaries

Laparoscopic or transvaginal ovarian drilling, commonly known as ovarian diathermy or electrocoagulation, is an alternate therapy option. 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 has a diameter of 4 mm and a depth of 5–7 mm. The penetration takes place in 5 s. This method takes the place of cuneiform ovarian resection. Cuneiform resection, which was done before to the development of the ovarian drilling technique, results in adherences and surgical problems. The first transvaginal laparoscopy was carried out in 2001, while the first laparoscopic ovarian drilling was carried out in 1984. Both methods are applicable.**(45)**

Method

Two extra trocars and a conventional endoscope are used for laparoscopic ovarian cautery. With a setting of 40 W for 4–5 seconds, the entire length of the unipolar needle electrode is introduced into the ovary. The suggested procedure for ovarian drilling is the laparoscopic technique. In the peritoneal cavity, transvaginal hydrolaparoscopy is carried out using saline solution. The endoscope can examine the whole pelvic cavity because of its 30-degree angle.

Transvaginal laparoscopy (THL) is another method for doing salpingoscopy with fallopian tube and fimbriae inspection . With roughly ten perforations in each ovary and a 10 mm depth of insertion, bilateral ovarian drilling was carried out. Spinal anaesthesia can be used to implement this approach. Ovarian drilling carries the same hazards as any surgical operation, including the possibility of adhesion formation. Safety may be impacted by the procedure selection (laparoscopy versus THL) . The THL is quicker, less prone to adhesions, and better tolerated by patients (reduced discomfort following surgery). The installation of saline solution, the shorter time, the use of bipolar diathermy, and the decreased bleeding since there is less ovarian manipulation than with a laparoscopy could be the reasons underlying these advantages. For obese women, THL is also a simpler method . 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. The peritoneal integrity will be verified by a second-look laparoscopy. **(46)**

Action mechanism

We still don't fully understand how ovarian drilling works. Ovarian drilling appears to decrease intraovarian androgen levels and hinder local androgen production, which lessens the inhibitory influence on follicular maturation. Lower testosterone levels reduce the positive feedback on LH secretion as well as the peripheral conversion of androgen to oestrogen. New follicular recruitment can occur naturally or with exogenous FSH stimulation. Acne, hirsutism, irregular periods, ovulation, and pregnancy are all improved by this method. Ovarian drilling eliminates the danger of multiple pregnancies and OHSS and does not require ultrasound monitoring. According to moderate-quality evidence presented in a Cochrane review in 2020, laparoscopic ovarian drilling likely lowers the number of multiple pregnancies and may lead to fewer OHSS. The literature varies on the effectiveness of ovarian drilling. There have been reports of ovulation and pregnancy rates of 30 to 90% and 13 to 80%, respectively. High LH concentration (>10UI/l), short infertility duration (<3 years), age (<35 years), and low antral follicle count (<50) are factors that increase the technique's effectiveness. Insulin resistance, elevated testosterone levels, and a BMI (>35 kg/m2) are detrimental to the efficacy

of this treatment The outcomes may also be impacted by the technique used. Giampaolino et al. (2018) showed that ovulation took place in 82.9% of the patients in the first 6 months after THL, which is related with a 70% pregnancy rate . The long-term maintenance of ovarian drilling's effects is another significant advantage, in addition to its effectiveness in terms of pregnancy rate. In fact, research indicates that over 60% of patients will see symptom improvement or remission for up to 20 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 study conducted in 2020, Debras et al. shown that ovarian drilling has long-term effects and allows for spontaneous conception. An AFC of less than 50, an age of less than three years, a normal body mass index (BMI), and an infertile time of less than three years were the prognostic criteria for this effectiveness. **(47)**

CONCLUSION

The pathogenesis of anovulation and early pregnancy failure in women with PCOS has enjoyed considerable attention, both in basic research and in clinical trials, over the past few decades. However, although a large body of information is now available, the exact mechanisms underlying the reproductive dysfunction are still not clearly understood. Multiple abnormalities have been identified. Folliculogenesis is disturbed and steroidogenesis is often abnormal. Gonadotrophin secretion might be increased—as is often the case with LH—or decreased—as has been reported with FSH.This can be due to abnormal steroidogenesis but whether the initiating factor is the gonadotrophin disturbance or whether the abnormal steroidogenesis precedes this is still uncertain. Hyperinsulinaemia and obesity are common in PCOS and impact on ovarian function. These abnormalities might affect endometrial receptivity. In addition, derangements in paracrine and autocrine function have been described in PCOS. It seems likely that multiple factors interlink to form part of a vicious cycle of abnormal folliculogenesis, inappropriate oocyte maturation, abnormal steroidogenesis, decreased endometrial receptivity and, as a consequence, anovulation or early pregnancy loss. Exactly what initiates the pathological process remains to be defined. In addition, the influence of advanced maternal age, the well-described background miscarriage rate in healthy women and the prevalence of chromosomal abnormalities in early miscarriages need to be considered when reviewing pathogenesis. Reproductive success contributes considerably to quality of life and the failure to conceive, which is common in PCOS, and the subsequent early pregnancy loss are obviously difficult for the patients concerned. Given the complexity of the condition, and the many background factors that can impact on ovarian function, before new management strategies are recommended, good clinical trial data are essentialcomplete evaluation of the infertility is needed to exclude other causes of infertility. PCOS treatment is still controversial but three lines of therapies were discussed. The first line of treatment remains lifestyle modifications and bariatric surgery-associated or not with metformin and myoinositol. Clomiphene citrate and letrozole are considered also as the first line of treatment. Gonadotrophin therapy and ovarian drilling are the second line of treatment. Nevertheless, the place of transvaginal hydrolaparoscopic ovarian drilling is still not well clarified. Further studies are necessary to encourage this technique. If the patient is still resistant to those therapies, a third-line of treatment is proposed as in vitro fertilization and in vitro maturation.

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