Infertility riding on Polycystic Ovarian Syndrome (PCOS): A review of treatment modalities

Abstract

Polycystic ovarian syndrome (PCOS) is the commonest cause of anovulatory infertility. Depending on the population studied between 5 and 18% of women of reproductive age suffer from PCOS, however not all of them are anovulatory or experience subfertility. PCOS has been associated with numerous reproductive and metabolic abnormalities. Despite enormous advances in the management of reproductive dysfunction, insight into the metabolic implications of PCOS is limited by the lack of uniform diagnostic criteria, the heterogeneity of the condition and the presence of confounders including obesity. Obesity clearly has a role in long term health and may best predict both reproductive and metabolic dysfunction as well as negatively affect the response to treatment in women with PCOS. Diabetes, cardiovascular disease and cancer are also at the forefront of any risk assessment or comprehensive treatment strategy for these women. Lifestyle modifications including dietary changes, increased exercise and weight loss are appropriate first line interventions for many women with PCOS. Pharmaceuticals including metformin, lipid lowering agents and oral contraceptives should be tailored to the individual's risk profile and treatment goals. The fertility treatment in women with subfertility and PCOS aimed to safely induce monofollicular ovulation resulting in the birth of a singleton child. Women with PCOS undergoing fertility treatment are at risk of multi-follicular development as well as ovarian hyper-stimulation syndrome (OHSS), so they must be carefully counselled and monitored during fertility treatment. It is imperative that prior to embarking on fertility treatment, a patient's health and weight is optimised. This chapter will explore the latest evidence for fertility treatments for women with PCOS.

Key words: Polycystic ovary syndrome, Awareness, Lifestyle modification

Introduction: Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. (1)

Manifestation can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia).

Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development, microcysts in the ovaries, anovulation, and menstrual changes. (2) Women with PCOS are at increased risk of metabolic problems (impaired insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus and cardiovascular disease), reproductive abnormalities (infertility, hyperandrogenism and hirsutism) and psychiatric illness (anxiety, depression and poorer quality of life). Anovulation is the predominant cause of infertility in PCOS. (3) This health condition is estimated to affect about 10 million women globally (4). One in every 10 women in India has polycystic ovary syndrome (PCOS), a common endocrine system disorder among women of reproductive age(5). According to a study by PCOS society, out of every 10 women diagnosed with PCOS, six are teenage girls.(5) A study conducted by the department of endocrinology and metabolism, AIIMS, shows that about 20-25 per cent of Indian women of childbearing age are suffering from PCOS. About 70 per cent have insulin resistance, 60-70 per cent have high level of androgen and 40-60 per cent have glucose intolerance.(6) In studies conducted in South India and Maharashtra, prevalence of PCOS was reported as 9.13 per cent and 22.5 per cent, respectively(4). The incidence of PCOS among women and teenage girls has risen to such an extent that the Indian Council of Medical Research (ICMR) has taken up a nationwide survey.(7) It is dangerous and alarming to note that if this condition is left unchecked or undiagnosed, it can lead to infertility among other long-term health concerns. (8) This is mostly due to unhealthy lifestyles, unhealthy diets and lack of exercise. Early diagnosis and treatment are key interventions which can prevent health problems. PCOS was described as early as 1935, but even after so many years, there is a general lack of awareness regarding the condition in India and it often remains undetected for years.(7)

Etiology: The main cause of PCOS is unknown both environmental and genetic factors are implicated. Causes of PCOS can be many such as: (9)

- Raised levels of insulin
- Hormonal imbalance
- Contraceptive pills
- Strong stimulation in adrenal in childhood
- Sedentary lifestyle/ Obesity
- Hereditary factors
- Stress
- Diabetes
- Hyperprolactinemia
- Cushing's syndrome
- Congenital adrenal hyperplasia

Pathophysiology: Despite being one of the most common endocrinopathies, a comprehensive explanation of pathophysiology is still lacking. The heterogeneity of PCOS may well reflect multiple pathophysiological mechanisms, but the definition of each contributing mechanism has been slow to emerge. Traditionally, it has been useful to consider the polycystic ovary syndrome as the result of a 'vicious cycle', which can be initiated at any one of many entry points. Altered function at any point in the cycle leads to the same result: ovarian androgen excess and anovulation. Several theories have been proposed to explain the pathogenesis of PCOS:

- A unique defect in insulin action and secretion that leads to hyperinsulinemia and insulin resistance.
- A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude.
- One of the hallmarks of polycystic ovary syndrome (PCOS) is increased ovarian androgen secretion that contributes to the ovarian, hormonal, and metabolic features of this condition. Thecal cells from women with PCOS have an enhanced capacity for androgen synthesis.
- An alteration in cortisol metabolism resulting in enhanced adrenal androgen production.

It must be accepted, however, that each of these are artificial stating points to our understanding of the metabolic–ovarian– pituitary circuitry being closely inter related. (10)

Pathophysiology of PCOD
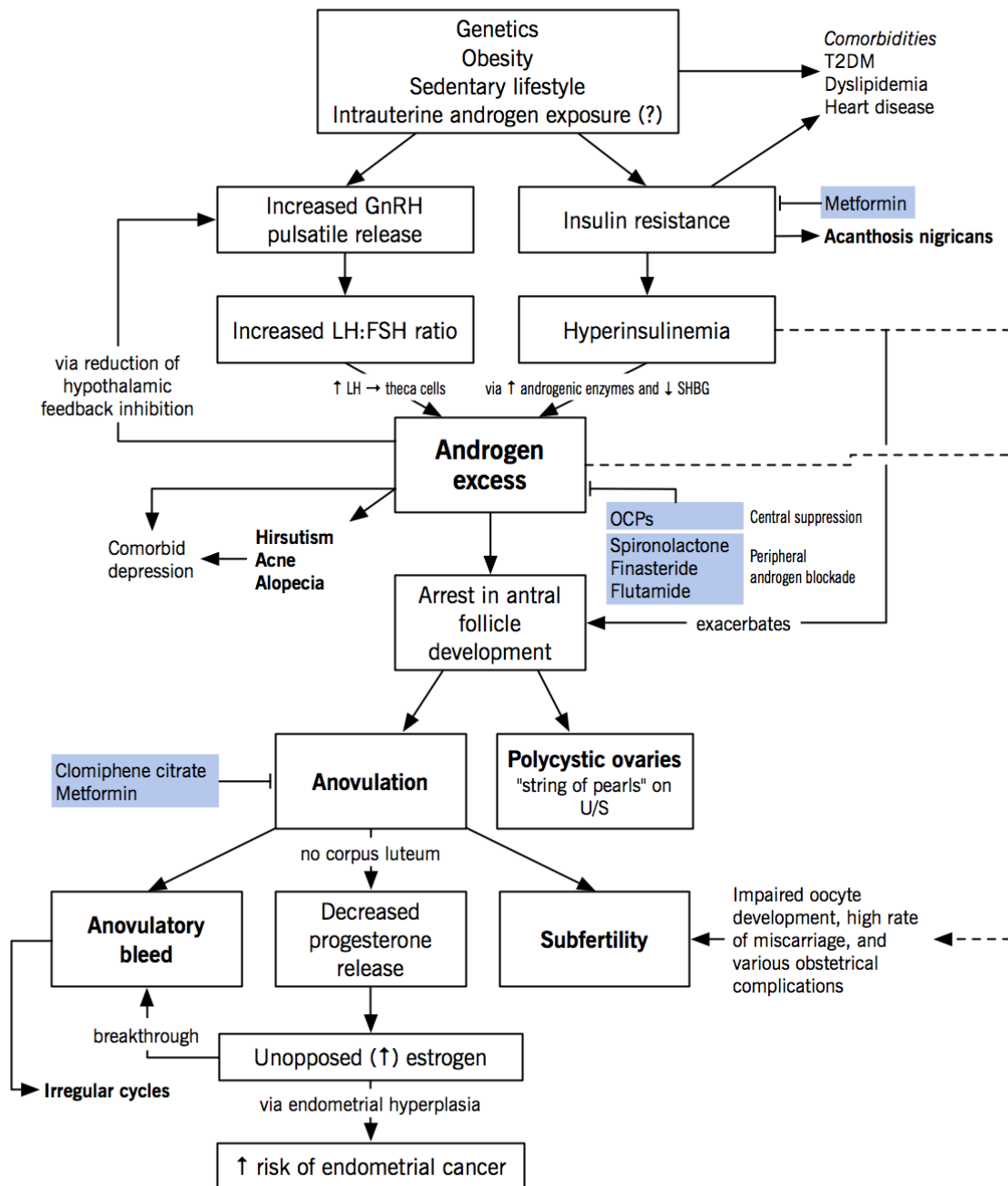
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Chart 1. Pathophysiology of PCOD

Clinical features: They vary from women to women. (11) Some of them are as follows:

1. Infertility- by preventing ovulation. (12)

2. Irregular, scanty, absent menses

3. Oligomenorrhea [85-90% of women]

4. Hirsutism

5. Acne, oily skin, dandruff

6. Depression or anxiety

7. Pelvic pain

8. Hair loss or male pattern baldness (13)

9. Weight gain or obesity (14)

10. Metrorrhagia

13. Swollen breasts before period

14. Bleeding with uterine fibroids during menses

15. Neuralgic pain during menses

16. Hysteria

17. Itchy vagina and vulva

18. Heavy periods

19. Sleep apnoea

20. Cysts on ovaries

21. Skin tags

22. High blood pressure (15) (16)

PCOS is a common hormonal disorder that can occur any time in women's life. Its effect depends on when it occurs. PCOS caused during adolescence and adulthood will cause reduced or no menses, polycystic ovaries, obesity, and excess sex hormone levels. Whereas if caused in ageing individuals it causes diabetes, high blood pressure, abnormal blood lipid i.e. cholesterol level also called as metabolic syndrome (17) The term "Syndrome XX" has been coined as name for PCOS. (18)

Diagnosis: Clinician use various methodologies to reach a diagnosis of PCOS which include the following but are not limited to:

- **Medical history**: Menstrual periods, weight changes and other symptoms are observed.
- **Physical Examination**: Measure blood pressure. Body Mass Index [BMI], and waist size, checking the areas of increased hair growth for Hirsutism.
- **Pelvic Exam**: Examination for enlargement of ovaries or swollen by increase number of cysts.

- **Blood Test**: Blood test for hormone androgen and glucose levels.
- Vaginal ultrasound sonogram/sonography

Treatment

PCOS has serious clinical sequelae including reproductive manifestations, metabolic complications and psychological problems (Figure 1) (19).

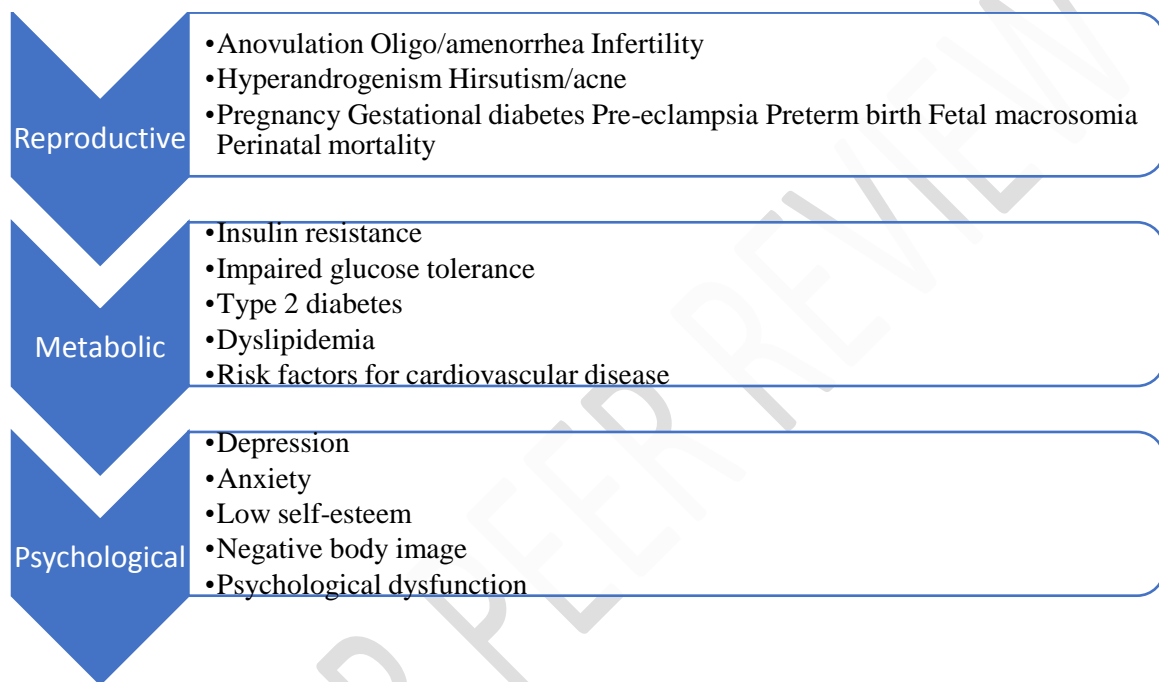| Reproductive	• Anovulation Oligo/amenorrhea Infertility • Hyperandrogenism Hirsutism/acne • Pregnancy Gestational diabetes Pre-eclampsia Preterm birth Fetal macrosomia Perinatal mortality
Metabolic	• Insulin resistance • Impaired glucose tolerance • Type 2 diabetes • Dyslipidemia • Risk factors for cardiovascular disease
Psychological	• Depression • Anxiety • Low self-esteem • Negative body image • Psychological dysfunction

Figure1: Clinical Sequelae of Polycystic Ovary Syndrome

The primary Etiology of PCOS is still largely unknown and a complex of genetic and environmental contributors combined with other factors including hypothalamic pituitary dysfunction, insulin resistance and hyperandrogenism are likely to contribute to the pathophysiology of the condition (19,20). Infertility is a prevalent presenting feature of PCOS with approximately 75% of these women suffers from infertility due to anovulation (21). Infertile women with PCOS undergo a thorough infertility work-up to look for causes of infertility other than anovulation. Where the only cause is anovulation, a number of infertility treatments have been proposed (Figure 2) (22).

Lifestyle (weight reduction if overweight or obese)	Pharmacological	Surgical	IVF
•Diet •Exercise	•Clomifene citrate •Metformin •Aromatase inhibitors •Gonadotropins	• Laparoscopic ovarian drilling •Bariatric surgery	•Usually indicated as third-line medical treatment or in the presence of other infertility factors

Figure 2: Treatments for anovulation in polycystic ovary syndrome.

Non-Pharmacological Approaches:

Lifestyle modification: Women with PCOS are usually obese (body mass index $>25kg/m^2$) and about 80% of obese women with PCOS have hyperinsulinemia (23). Hyperinsulinemia and increased growth factors stimulate the production of fat cells centrally, leading to an increased waist/hip ratio. Obese women with PCOS have lower pregnancy rates in ovulation induction cycles and higher miscarriage rates than those women who are a healthy weight (24, 25). These women require higher doses of medication, tend to have a multi-follicular response, and have a higher chance of multiple pregnancy and cycle cancellation (25,26). A small to moderate weight loss, restores menstrual cycles, improves ovulatory function, and increase pregnancy rates through a decrease in insulin resistance (27). This was shown by Clark et al, (28) who presented 6-month, follow-up on patients who underwent a lifestyle modification program. Of 67 patients with a BMI $>30kg/m^2$ who followed the program and had failed to conceive in the past, 60 patients ovulated and 52 patients became pregnant, compared with none in the reference group. Further there were reduction in miscarriage rates. Lifestyle change is the first line treatment for women with PCOS who are overweight or obese with as little as 5–10% weight loss has significant clinical benefits (29) in improving psychological outcomes, reproductive features (menstrual cyclicity, ovulation and fertility) and metabolic features (insulin resistance and risk factors for cardiovascular disease and Type 2 diabetes mellitus) (30). An expert international panel of PCOS researchers appointed by the Androgen Excess and PCOS Society recently reviewed the literature on the lifestyle management (dietary, exercise or behavioural interventions) of PCOS and concluded that lifestyle management should be the primary therapy for the treatment of metabolic complications, and may improve ovulatory function and pregnancy in overweight/ obese women with PCOS. The latter conclusion on reproductive outcomes was based on 13 uncontrolled observational studies and a single RCT showing a nonsignificant increase in ovulation with lifestyle treatment (31).

Pharmacological Approaches:

Ovulation Induction: Because oligo-ovulation or anovulation is the main reason for infertility. In PCOS patients, the goal of treatment in those, seeking for pregnancy is to maintain the development of single follicle and restore normal ovulation. For lean women with PCOS or those women for whom lifestyle intervention are ineffective to restore ovulation, oral medications to treat anovulation are considered the second-line treatment. (32) The two most commonly prescribed oral ovulation induction agents are clomiphene citrate and metformin. (33)

Clomiphene citrate: Clomiphene citrate is the oral ovulation induction agent of choice (34). It blocks oestrogen receptors at the level of the hypothalamus, which alters gonadotropin-releasing hormone secretion and leads to an increase in follicle-stimulating hormone and ovulation. It has high ovulatory rates when given at the proper dosage (35). Clomiphene is administered during the early follicular phase the menstrual cycle or during a progesterone-induced withdrawal bleed. It is important to assess for evidence of ovulation to ensure that a woman has an opportunity for pregnancy. A luteal progesterone level greater than 3ng/ml is consistent with ovulation. For women who do not ovulate on the starting dosage of clomiphene citrate, the clinician may increase the daily dose. A change in therapy is recommended if a pregnancy does not occur after six ovulatory cycles on the drug. (22). Clomiphene citrate has antiestrogenic properties which can cause damage to cervical mucus and endometrial thickness, which may negatively affect conception and implantation. Literature states that (36) approximately 80%- 90% of patients are reported to have evidence of ovulation, but only 30–50% of them become pregnant. The discrepancy between the ovulation rate and pregnancy rate may be due to the effects of androgens on the oocytes, leading to poorer oocyte quality; the long half-life of clomiphene citrate, which has a negative impact on the endometrium and cervical mucus due to the anti-oestrogen effect; or the increased incidence of premature LH surge in patients with PCOS. Therefore, monitoring of follicular growth by ultrasound and tracking LH levels to ascertain ovulation and to maximize the efficiency of each cycle is strongly recommended. If Preovulatory follicle >19mm in diameter in the absence of a LH surge, human chorionic gonadotropin (hCG) is given, although the routine use of hCG does not improve pregnancy rates. (37) Recommendation to further treatment depends on patients age, i.e., treatment after 3–6 months of clomiphene citrate with documented ovulation, as 75% of the pregnancies, achieved with clomiphene citrate occur within the first three cycles. (38)

Letrozole: Letrozole is a selective, reversible, orally administered aromatase inhibitor. As it suppresses oestrogen biosynthesis, it stimulates the release of FSH from the pituitary and induces ovulation. The letrozole has relatively short half-life in comparison with clomiphene citrate and have fewer negative effects on the endometrium and cervix. (39) 75% of women who had failed to ovulate on clomiphene citrate achieved ovulation with letrozole, with a 25% pregnancy rate. According to a study done by Ahmed Walid A. Morad *, Mohamed A. Elhadi Farag in Egypt in 2014, the use of letrozole in place of clomiphene citrate, increases endometrial thickness, trilaminar pattern and improved endometrial perfusion based on Doppler study of spiral arteries comparing the letrozole and clomiphene citrate for ovulation induction. (40) Another study conducted by Yue Zhao, Xiangyan Ruan and Alfred O. Mueck at Beijing and published in 2017 stresses the fact that LTZ combined with low-dose Hp-HMG is an effective and safe choice for reducing hyperstimulation and increasing pregnancy rate in CC-resistant women with PCOS.(41) Letrozole is given at a dosage of 2.5–7.5 mg/day on cycle days 3–7 and can also be given as a single 20mg dose.(42) Letrozole can also be used in conjunction with gonadotropins and reduces the dose of gonadotropins required for stimulation, as well as the risk of ovarian hyperstimulation, by reducing the serum estradiol level.(43) In addition, letrozole at a dosage of 5 mg/day led to higher pregnancy rates and better follicular development.(44) medications are well tolerated with headaches and fatigue being the most common adverse effects. Aromatase inhibitors have the advantage of a short half-life, are inexpensive compared with gonadotropins, and may be effective for mono follicular ovulation induction, with a low risk of ovarian hyperstimulation syndrome.

Insulin- Sensitizing agents: Metformin is a biguanide, insulin sensitizing agents restore ovulation in PCOS is due to insulin resistance with compensatory hyperinsulinemia, which is the prominent feature of PCOS. (45) Hyperinsulinemia is caused due to increase ovarian androgen biosynthesis in vivo and in vitro and decreased sex hormone-binding globulin synthesis from the liver, leading to increased bioavailability of free androgens. This excess in local ovarian androgens production enhanced by hyperinsulinemia causes premature follicular atresia and anovulation. (46) In patients with PCOS, metformin has been shown to be beneficial in reducing hyperinsulinemia and hyper androgenemia while facilitating normal menses and pregnancy. (47,48,49-52) Metformin is the first-choice insulin-sensitizing agent because of its safety in pregnancy and benefit of weight loss; other agents are reserved for those who cannot tolerate metformin. Metformin is contraindicated in women with impaired renal function. Serum creatinine levels are measured and if levels are

≥1.4 mg/dL use of metformin is abandoned. This is the level at which an increased risk of lactic acidosis and increased creatinine levels in patients undergoing radiologic procedures involving administration of intravenous contrast material has been shown. (53) Common gastrointestinal adverse effects including nausea, bloating, flatulence, and diarrhoea, the frequency of which can be reduced by initiating metformin at a low dosage and slowly increasing the dosage upward to the preferred 1500–2000 mg/day, taking metformin with food, and using extended-release formulations. There is convincing evidence that metformin monotherapy is effective in inducing ovulation in patients with PCOS and that metformin is also beneficial when used in conjunction with clomiphene citrate. (54,55) Metformin used in obese women with PCOS show high ovulation rates, decrease in insulin levels, and improvements in insulin sensitivity. (47,48,49-52,55)

Metformin with Gonadotropin: When metformin and clomiphene citrate combination is unsuccessful, the next step is low-dose gonadotropin treatment. The sequential treatment of metformin and clomiphene citrate is effective in improving ovulation and pregnancy rates in clomiphene citrate-resistant patients with PCOS, with a reduction of cost to the patients. (56) Therefore, metformin and clomiphene citrate combination are tried before gonadotropin treatment. The risk of gonadotropin in women with PCOS include increased multi-follicular ovulation and the subsequent increase in multiple births and ovulation hyperstimulation syndrome. (57,58) Administration of low-dose gonadotropins (50–100IU recombinant FSH) in a low and slow protocol has been shown to be successful. (58,59) Metformin treatment may be beneficial in women with PCOS undergoing gonadotropin stimulation. Co-treatment of metformin has been shown to improve the ovarian response to exogenous gonadotropin in women with clomiphene citrate-resistant PCOS. (60) Metformin co-treatment showed a more orderly growth of follicles and a reduction in multi-follicular development. We also found a more orderly ovarian stimulation in women with PCOS undergoing in vitro fertilization (IVF) who had received metformin pre-treatment. (61) There appeared to be a shift in follicle size in the metformin group with a reduction in the number of small follicles in the recruited cohort.

In Vitro Fertilization: First and second line in infertility management in women with PCOS is ovulation induction therapies, anovulation and no other fertility factors. Failure of ovulation induction therapies and inadequacy to overcome other concomitant causes of infertility means that ART therapies, including IVF and ICSI, used in male factor infertility, plays important role in PCOS. There are risks and limitations, but IVF still offers the opportunity for pregnancy and live births. As there are diversity of protocols available for IVF challenges exist across and concerns in PCOS including OHSS, high oestradiol levels,

accelerated endometrial maturation and optimally the use of 'freeze all' interventions. The clinical practice questions regarding indications, timing and comparative efficacy with other treatments, yet RCTs in this area are very limited in women with anovulatory PCOS. (62)

Metformin with Gonadotropins in patients undergoing In vitro fertilization:
After the unsuccess with gonadotropin treatment, next step is IVF. Not many studies explore the role of pre-treatment with metformin in patients with PCOS undergoing IVF. In non-randomized studies by Stadtmauer et al., (63,64) metformin pre-treatment improved the ovarian stimulation compared with gonadotropin alone. There was no change in the amount of gonadotropin used, but more mature oocytes were retrieved with lower peak estradiol levels, and a higher number of embryos obtained in the metformin-treated group. The result of study also showed improved clinical pregnancy rates in the metformin-treated groups. Patients with PCOS were clomiphene citrate resistant and heterogeneous with regard to insulin resistance. A study under taken by Fedorcsak et al., (65) investigated a small group of insulin-resistant obese patients with PCOS in a randomized crossover study. Patients with PCOS had an average BMI that was significantly higher than that reported in the Stadtmauer et al. (63,64) studies (32 kg/m2 vs 26 kg/m2). The study showed that there is no difference in gonadotropin requirement compared with using gonadotropin alone but there is increase in the mean number of mature oocytes recovered in patients with PCOS with insulin resistance. Study was unable to predict about pregnancy rates because of the crossover design of the study and because of the small number of patients enrolled. In the study that was randomized, double-blind, placebo-controlled, studied metformin pre-treatment in conjunction with gonadotropins prior to IVF, (66) the study revealed no significant differences in ovarian stimulation or pregnancy rates with metformin, except a trend toward higher pregnancy rates in the group of lean women. The results of all the studies showed very good pregnancy rates with IVF in patients with PCOS who were treated with metformin and in those treated with diet and lifestyle changes without metformin. All the studies propose that there may be a subset of patients with PCOS that benefit from metformin, which may be related to pre-existing insulin resistance or BMI, and obesity independently plays a role in IVF success. This is congruous with the other findings that metformin does not improve the reproductive and endocrine outcomes in extremely obese patients. (67) As the results of IVF are good with the treatment with metformin along with a hypocaloric, carbohydrate-modified diet and lifestyle changes, these patients with PCOS are pre-treated with metformin prior to IVF, although this is not based on randomized controlled trials. There is lacuna a demand for more

randomized controlled trials that should how the benefits of metformin use in patients with PCOS who are undergoing IVF.

Ovarian stimulation with Follicle Stimulating Hormone (FSH)/ Luteinizing

Hormone versus recombinant FSH: Patients of PCOS have high levels of LH, which are inimical to follicle development and increase miscarriage rates. (68) Therefore, theoretically exogenous supplementation of LH could be deleterious. The studies on PCOS patients which compared the administration of menotropins with recombinant FSH have not shown an increase in follicular phase serum LH levels with menotropins and actually decreased the LH/FSH ratio. (69,70) In addition, certain IVF studies did not show any difference in ovulation and pregnancy rates or in any stimulation parameters when comparing the use of menotropins with purified FSH. (71,72) The clinical results of treatment with menotropins and purified FSH in patients with PCOS were comparable when administered in a low-dose regimen in ovulation induction studies. (73) The patients with PCOS on treatment with menotropins miscarriage rates were not increased. According to a Cochrane review there were no differences in pregnancy rates between treatments and effectiveness of menotropins versus purified FSH. However, the use of FSH was associated with a decreased risk of ovarian hyperstimulation syndrome. (74) The use of purified FSH preparations offers an advantage over menotropins in patients with PCOS only with regard to the ovarian hyperstimulation syndrome risk.

Other Treatments

Surgical treatment for Ovulation Induction: Earlier women with PCOS were treated with bilateral ovarian wedge resection leading to resumption of menstrual cycles and pregnancies as reported in initial report from Stein and Leventhal. (74). Initially the pregnancy rates were 85% but the later reports show less success, and raised the concerns about procedure that were invasive and there was risk of periovarian adhesions. The advancements in laparoscopic techniques resulted in renewed interest in ovarian drilling, with the expectation that there is a decreased likelihood of adhesions and morbidity in this technique. There are multiple studies which proved the success of using methods employing electrocautery, lasers, and the harmonic scalpel, with equivalent success rates with restart of ovulation and menstrual cyclicity in approximately 80% of patients. (76-84) In these techniques thermal damage and necrosis is done to destroy the androgen-producing ovarian stroma by drilling holes in each ovary. The result is long-term with the reduction in intraovarian androgen production, LH pulse amplitudes, and also shows effect on the pituitary-ovarian axis. But it does not show any improvement in insulin sensitivity. One of the

long-termed follow-up studies reported that that 84% of women were still ovulating 20 years after surgery and that androgen levels stayed normalized. (82) Donesky and Adashi(81) reviewed 29 reports of laparoscopic ovarian diathermy and calculated an aggregate ovulation rate of 84% from that group of studies, with a pregnancy rate of 55% in a total of 729 patients. Sixty-eight percent of treated patients achieved pregnancy within 12 months of treatment and 73% became pregnant within 24 months. (78) The majority of pregnancies were seen within the first year of surgery. In a long-term, follow-up study in 116 anovulatory patients who underwent laparoscopic ovarian drilling, 55% of women continued to ovulate beyond the first year after laparoscopic ovarian drilling. (83) Based on the high pregnancy rates reported in these studies, adhesion formation after laparoscopic ovarian drilling, it does not appear to impact on the achievement of pregnancy. Several studies were conducted after this procedure using a second-look laparoscopy and reported that adhesion risks range from 20% to 80%. (85-87) A meta-analysis concluded with insufficient evidence to determine a difference in pregnancy or ovulation rates in clomiphene citrate-resistant patients undergoing ovarian drilling or gonadotropin therapy. (88) The advantages of laparoscopic treatment is its long-term effects and repetitive ovulatory effects from a single treatment, reductions in the risks of multiple pregnancies and ovarian hyperstimulation syndrome, and a decrease in hyperandrogenemia. However, when compared with metformin use, the advantages do not overcome the risks of laparoscopy, general anesthesia, periadenexal adhesion formation, and premature ovarian failure. This inference was supported by a recent randomized, double-blind, placebo-controlled study which compared the effectiveness of laparoscopic ovarian drilling with metformin administration without surgery in the treatment of clomiphene citrate-resistant women with PCOS.(89) This study established that there is equivalent ovulation rates with the two treatments, with improved pregnancy rates and lower rates of miscarriage in patients who received metformin treatment compared with patients who had undergone ovarian drilling.

Conclusion: PCOS is the most common cause of anovulatory infertility and thus is responsible for a large percentage of women seeking fertility treatment. When implementing a treatment plan for a patient with PCOS their metabolic health and weight are important factors that must be considered in selection of patients. IVF is planed only for patients following unsuccessful ovulation induction or other specific fertility issues. For very high-risk patients of in vitro oocyte maturation Pre-treatment with Metformin is done and it continue through IVF cycle. Managing the cycle and monitoring the cycle is individualised stimulation regime. The risks of OHSS and multi-follicular development in patients with

PCOS means that care must be taken with close, careful monitoring to ensure mono-ovulation is achieved and the risks of multiple pregnancy and OHSS is kept to a minimum. If this approach is adopted the infertility treatment for these women is both safe and effective and patients should be reassured of these facts. (90)

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