

Clinical Approach to Infertility due to PCOD

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PCOD is most common endocrine disorder in women of reproductive age group with prevalence of about 5 - 10%. clinical prod may present as ovulatory dysfunction in the form of oligo-menorrhoea or amenorrhoea, hyperandrogenism and PCOD morphology on sonography classically this combination of symptoms were described by Stein and Levanthal in 1935 [1]. Approximately 80% cases of anovulatory infertility are due to PCOD.

Rotterdam 2003 criteria entails following components for diagnosing prod as [2]:

1. Oligo and or an ovulation
2. Clinica and or biochemical signs of hyperandrogenism.
3. Polycystic ovaries on ultrasound.

Of these two of the 3 criteria are needed for diagnosing prod.

Polycystic ovarian morphology is twelve or more antral follicles (2 - 9 mm in diameters) in either ovary, an ovarian volume of > 10 ml in one or both the ovaries offers best specificity and sensitivity for diagnosing PCOD. exclusion of others causes of hyperandrogenism such as bushings syndrome, congenital adrenal hyperplasia must be done by appropriate investigations.

Obesity, hyperandrogenism and insulin resistance are the factors that influences the symptom expression of PCOD. Anovulation is most common in women with prod accounting for 80 - 90% of WHO. Group ii anovulatory infertility.

According to American society of reproductive medicine, the evaluation of infertility in women with PCOS should start after 6 months of regular unprotected sexual intercourse.

Treatment of infertility in cos patient includes non-pharmacological measure as weight reduction, lifestyle modifications, preconception counselling, and pharmacological agents with the of monofollicular or bifollicular growth and ovulation.

Lifestyle modification with weight reduction of 5 - 10% of body weight reduction [3] is associated with central obesity improvement, improved ovulation rate and hyperandrogenism correction. In addition to this body weight reduction is associated with reduced incidence of pregnancy complications and that during neonatal periods.

Women with PCOS have an increased risk of congenital anomalies in babies including but not limited to heart and neural tube defects, gestational diabetes mellitus, preeclampsia, hypertensive disorders of pregnancy, miscarriage and preterm birth, preconception counselling with folic acid supplementation is of hell in these patients.

Factors that contribute to sub fertility in PCOD are anovulation, metabolic and inflammatory factors, effects of obesity, effects on oocyte quality and fatal development. Oocytes [4] from PCOD patients shows reduced compete for development and reduced ability to

complete meiosis and hyperandrogenism causes premature granulosa cell leutinsation, and impair cytoplasmic and nuclear maturation of oocytes. Also intrafollicular microenvironment is which is related to oocyte quality is affected by ovarian hyperandrogenism. Teissier, *et al.* showed higher intrafollicular testosterone levels in patients with PCOD.

First line of treatment in patient with PCOS with anovulation is Clomiphene citrate for ovulation induction, this drug is oestrogen receptor modulator acting both as oestrogen agonist and antagonist. When administered in early follicular development, it competes with oestrogen for its receptors in hypothalamus and pituitary blocking the negative feedback mechanism and increasing endogenous gonadotrophin release causing recruitment of follicles between 6th and 9th day of menstrual cycle.

Starting with the dose of 50 mg/day for 5 days from day 2 to day 5 of cycle, and dose may be increased upto 150 mg/day depending on ovarian response. The ovulation rate achieved with clomiphene can reach upto 75 - 80% with cumulative pregnancy rate of 60 - 70% and 22% conception rate per cycle. Discrepancy in ovulation rate and pregnancy rate can be explained by antiestrogenic effects of clomiphene on endometrium [5].

Advantages of clomiphene are low cost, oral administration and less monitoring needed. But clomiphene treatment should be limited to 6 cycles about 15% of women with clomiphene does not ovulate and are termed as clomiphene resistant, in which cases gonadotrophin and surgical approach in the form of ovarian drilling can be tried. In limited number of patient clomiphene it can cause flushing, headaches, visual disturbances and abdominal discomfort. And ovarian hyper stimulation in 1 - 6% of patients.

As hyperinsulinemia is an well-established feature in PCOS patients, use of insulin sensitising agent in the form of Metformin may improve ovulation rate in these patients. Metformin is oral biguanide is commonly used, it causes reduced hepatic gluconeogenesis and increases peripheral glucose utilisation. It is appears that Metformin is advantageous in reducing ovarian hyper stimulation syndrome.

Second line of treatment in patients who are resistant to clomiphene is done with gonadotrophins [6]. Before commencing treatment tubal patency needs to be assessed if not done earlier. Starting with very low dose (37.5 to 75 IU/day) and increasing according to response on sonographic serial measurement of follicular size. as gonadotrophin are costly rather than combining it with timed intercourse it needs to use for ovulation induction with IUI. It is associated with ovulation rate of around 70% and clinical pregnancy rate of 20% in natural timed intercourse.

PCOD drilling is required in some patients with PCOS this is also considered as second line modality but involving more cost and anaesthesia requirement. These punctures can be done either with monopolar cautery or using laser with 4 - 10 punctures [7]. As large number of punctures can be associated with premature ovarian failure. Drilling acts by decreased ovarian androgen secretion and consequently reduced peripheral aromatisation of androgen into estrones, also it causes micro follicular environment more estrogenic facilitating follicular growth. An ovulation rate of 54 - 76% can be achieved with ovarian drilling patients in 6 months period after the procedure with pregnancy rate of about 28 - 56%. If there is no ovulation for 3 months after the drilling ovulation induction with clomiphene need to be tried and if there are 6 anovulatory cycles after the ovarian drilling then gonadotropins need to be used for induction.

Ovarian drilling has some advantages as compared to gonadotropin as it is associated with low multiple gestation rates but as due to high cost of operation and requirement of anaesthesia its cost effectiveness is low as compared to gonadotropins, but in carefully selected patients it can be an alternative before IVF treatment and in clomiphene resistant cases.

IVF is third line of treatment for patients with PCOS. if patients presents with bilateral tubal block with oligo-spermia, count less than or equal to 5 million, IVF become first line of treatment along with lifestyle modification. In prod patients to avoid ovarian hyperstimulation, suppression of endogenous LH by GnRH agonist allows follicular development. GnRH antagonist [8] protocol for pituitary suppression hold promising in PCOS as they does not activate GnRH receptors and produces rapid suppression of gonadotropin secretions in short span off time as in hours. as it allows for short term treatments compared to long agonist protocols.

To conclude women with PCOS undergoing IVF cycles respond differently as compared to normal patients so lifestyle modification, weight reduction, along with graded management from clomiphene to gonadotropins and IVF helps to improve the success rates. before closing aromatase inhibitors are promising in causing mono follicular development and reducing antiestrogenic side effects associated with clomiphene and GnRH antagonist protocol appears to be safe allowing for GnRH agonist trigger and luteal phase support reducing the incidence of OHSS along with Metformin.

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