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Evidence Based Management of Infertility in Women with Polycystic Ovarian Disease

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Abstract

PCOS is the most common cause of anovulatory infertility. Life style changes is the first line treatment in management of PCOS. Even 5-10% weight loss has significant clinical benefits. Obesity is associated even with long-term metabolic outcome in children. Weight loss should be advised prior to conception. First choice of ovulation induction is clomiphene citrate (CC) use of metformin in PCOS should be restricted to the patients with glucose intolerance. Gonadotrophin with starting dose of 37.5-50 IU/day should be used in CC failure situation. Laparoscopic ovarian surgery (LOS) is preferred in CC resistant cases with persistently hypersecretion of LH. It can be alternative to gonadotrophin for CC resistant PCOS cases. Repeated LOS should not be encouraged. In >50% of LOS treated adjuvant treatment may be required. Addition therapy with CC can be instituted after 12 weeks and gonadotrophines may be considered after 6 weeks. After failure of all modalities IVF may be offered.

Key words: Infertility; Induction of ovulation.

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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting 4% to12% of reproductive age women.[1] Recently a community-based prevalence study based on the current Rotterdam diagnostic criteria has shown the prevalence to be 11.9%- 17.8%.[2]

PCOS is the most common cause of anovulatory infertility affecting 90% - 95% of women attending infertility clinics.[3] Factors implicated in the low fertility in these group of women include anovulation, increased risk of early miscarriage, and late obstetric complication such as gestational diabetes mellitus, increased weight gain and pre eclampsia.[4] Obesity is also a common finding in these women and appears to affect reproductive outcome as an independent factor.[5]

It should be noted that PCOS is a diagnosis of exclusion and conditions including thyroid dysfunction and hyperprolactinaemia should be excluded biochemically, while more rare conditions should be excluded clinically (Cushing's syndrome, virilising tumours, and so on).

Targeted approach to therapy

Management should focus on support, education, addressing psychological factors and strongly emphasising healthy lifestyle with targeted medical therapy as required. Treatment options need to be tailored to the clinical presentation and patient desire. Education on short-term symptoms and long-term risk factors of PCOS is important in allaying anxiety and minimising the impact of illness in chronic disease.

Lifestyle modification

Lifestyle change is the first line treatment in an evidence-based approach in the management of the majority of PCOS women [7]. Furthermore, prevention of excess weight gain should be emphasised in all women with PCOS with both normal or increased body weight. Weight loss of 5% to 10% has significant clinical benefits such as resumption of regular menses and restoration of ovulation. Incorporating simple moderate physical activity including structured exercise (at least 30 min/day) and low carbohydrate restricted diet increases weight loss and improves clinical outcomes in PCOS [5].

Obesity independently exacerbates infertility and reduces effectiveness of interventions. Maternal and fetal pregnancy risks are greater and long-term metabolic outcomes in the child are related to maternal weight at conception. Overweight women prior to conception should be advised for folate, smoking cessation, weight loss and optimal exercise, prior to additional interventions.[7,8]

Clomiphene citrate

Clomiphene Citrate (CC) remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS. CC is an estrogen antagonist that produces an increase in circulating follicle stimulating hormone (FSH) concentrations by negative feedback blockage, thereby inducing follicular growth and ovulation.[9]

The starting dose of CC generally should be 50 mg/day (for five days, starting on Day 2–5 following a spontaneous or progestin-induced withdrawal bleeding). The recommended maximum dose is 150 mg/day, as there is no clear evidence of efficacy at higher doses and six cycles can be performed.

Although monitoring by ultrasound is not mandatory to ensure good outcome , the practice in many centres is to monitor the first cycle to allow adjustment of the dose in subsequent cycles based to the observed response.[10] Approximately 75–80% of patients with PCOS will ovulate after CC .[11] Although there appears to be discrepancy between ovulation and pregnancy rates, life-table analysis of the largest and most reliable studies indicates a conception rate of up to 22% per cycle in those ovulating on CC. These differences in results are attributated to the antiestrogenic effects of CC. Treatment generally should be limited to six (ovulatory) cycles, second-line therapy with FSH or laparoscopic ovarian surgery (LOS) should be considered at that time Cumulative live birth rates vary between 50–60% for up to six cycles .[12]

Insulin sensitizers

Insulin resistance affects 10%-25% of general population, this finding together with hyperinsulinaemia appears to be present in a significant number of PCOS patients. [13] Approximately 10% of women with PCOS and no obesity could present insulin resistance.

Insulin sensitizers available include metformin, a biguanide, and the thiazolidinediones (pioglitazone and rosiglitazone). Metformin lowers glucose by inhibiting liver production without producing hypoglycaemia in normoglycaemic subjects, since it increases the number of receptors but not insulin secretion. Metformin improves insulin sensitivity and hyperandrogenism, increases SHBG concentration, lowers leutinizing hormone (LH) concentration and restores ovulation.[13]

At present, use of metformin in PCOS should be restricted to those patients with glucose intolerance. Although uncontrolled trials and case reports suggest that metformin is safe during pregnancy, it would be prudent to discontinue metformin when pregnancy is confirmed.[14] With regard to their use during pregnancy, metformin is a category B drug according to FDA, Pioglitazone and rosiglitazone are category C drugs.

The primary risk with metformin is lactic acidosis, which is only seen in high risk patients with renal, liver or congestive heart failure. [14] The major risk with the thiazolidinediones is liver toxicity, and recently there has been

concern about increased cardiovascular morbidity with rosiglitazone .[15]

Aromatase Inhibitors

Letrozole, an aromatase inhibitor, is the newest addition to our armamentarium in the treatment of infertility. It is utilized in much the same way as clomiphene citrate, but with some additional benefits.[16] Letrozole is not approved in India for this indication.

Letrozole is a third-generation aromatase inhibitor that works by inhibiting estrogen biosynthesis, thereby releasing the hypothalamus/pituitary from negative feedback and increasing the secretion of FSH by the pituitary allowing for greater follicular development. It also increases intrafollicular androgens [17] which in turn is thought to upregulate and sensitize FSH receptors in the ovary. The advantage of letrozole is that it avoids peripheral antiestrogenic effects on the endometrium, while stimulating monofollicular growth in the ovary.[18]

Letrozole is typically administered on days 3–7 of the menstrual cycle at doses of 2.5–7.5 mg/day in 2.5mg increments. For women with anovulatory infertility,in which only one or two ovulations are desired per month. Most studies utilizing letrozole at 2.5mg daily for 5 days show between one and two mature follicles grown at this dose. [18]Studies utilizing 2.5mg of letrozole versus 100mg of clomiphene for 5 days in the early follicular phase, found fewer mature follicles (1.2 vs 2.4) but higher pregnancy rates with letrozole use (22% vs 9%).[19] Another study found no differences in number of mature follicles (1.62 vs 1.63) for letrozole at 2.5 or 5mg on days 3–7 of the cycle versus clomiphene citrate at 100mg dosing, but a higher pregnancy rate at 19% versus 12.5%.[20]

It appears that letrozole, when used for clomiphene citrate naive or resistant anovulatory women, confers superior pregnancy rates. It could augment or even obviate the use of gonadotropins in the treatment of women who have been unsuccessful in achieving pregnancy with clomiphene citrate. Further studies are needed to determine optimal dosing and long term safety for women treated with the drug.[21] Currently this drug is not in use anymore for treating the above as its been banned in India.

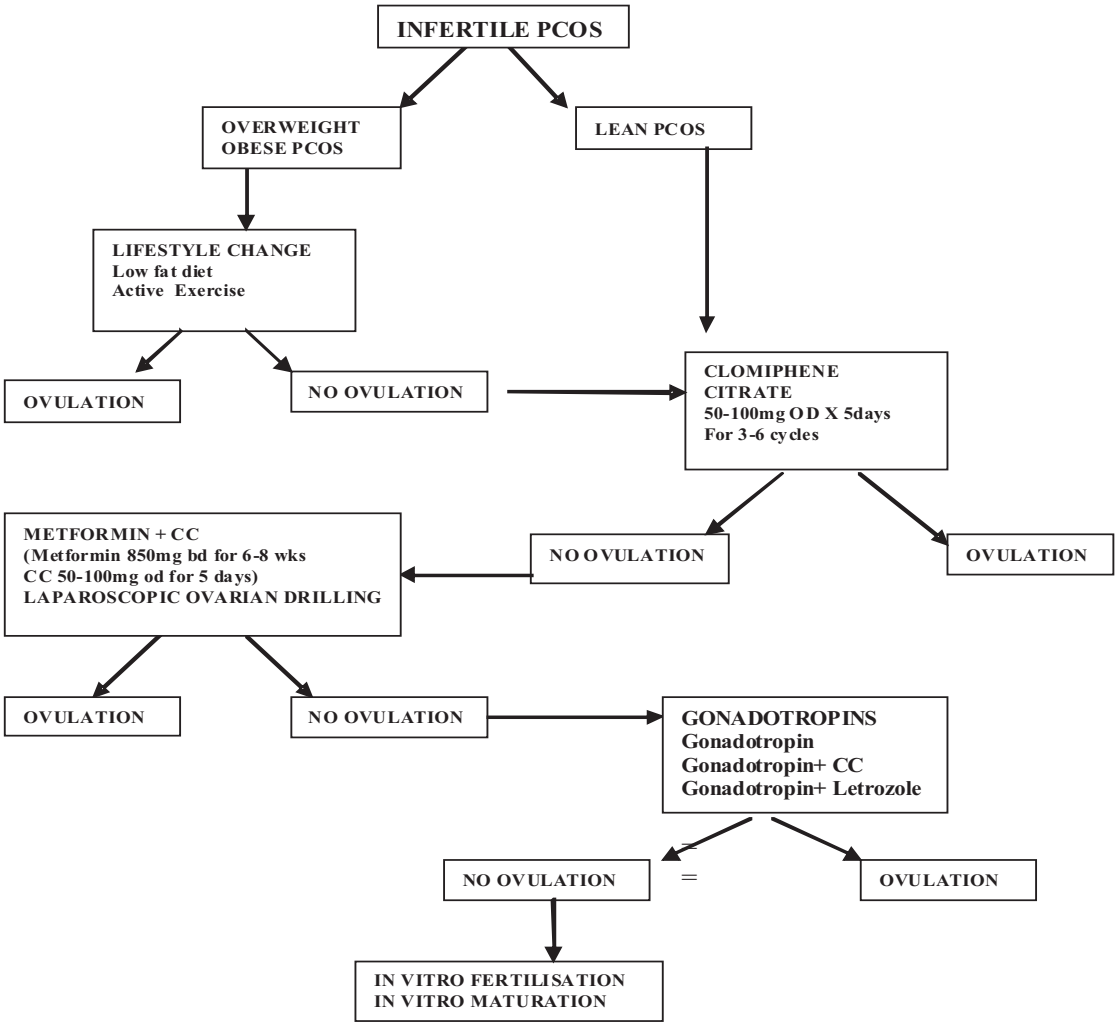
Gonadotrophins and GnRH analogues

The aim of ovulation induction for women with anovulatory PCOS is to restore fertility and achieve a singleton live birth. The method of ovulation induction using gonadotrophin therapy is based on the physiological concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles.[22]

The recommended starting dose of gonadotrophin is 37.5–50 IU/day. Adherence to a 14-day starting period at least for the first cycle is less likely to result in excessive stimulation. Small FSH dose increment of 50% of the initial or previous FSH dose are less likely to result in excessive stimulation and duration of gonadotrophin therapy generally should not exceed six ovulatory cycles. Intense ovarian response monitoring is required in order to reduce complication and secure efficiency. [23] Strict cycle cancellation criteria should be agreed upon with the patient before therapy is started. It would seem prudent to withhold hCG administration in the presence of more than two follicles >16 mm or more than one follicle >16 mm and two additional follicles >14 mm, in order to minimize the risk of multiple pregnancies in women with PCOS under the age of 38 without any other infertility factors.[22]

Overall, low-dose regimens result in a monofollicular ovulation rate of > 70%, a pregnancy rate of 20% and a multiple live birth rate of 5.7% Correspondingly, there is a low incidence of multiple pregnancies (<6%) and OHSS (<1%). [24]

The concomitant use of a GnRH agonist with gonadotrophin administration to improve pregnancy rates in patients undergoing ovulation induction has not been firmly established, moreover combined therapy was



associated with an increased risk of OHSS. Therefore, the significantly higher hyperstimulation rate, the associated risk of multiple pregnancies and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not justify the routine use of GnRH agonists during ovulation induction with gonadotrophins in PCOS patients.[22]

Laparoscopic ovarian surgery

Multiple ovarian puncture performed either by diathermy or by laser is known as 'ovarian drilling'. The main indication for LOS is CC resistance in women with anovulatory PCOS. LOS also may be recommended for patients who persistently hypersecrete LH, either during natural cycles or in response to CC, because it may reduce LH secretion. In addition, LOS may be useful in anovulatory women with PCOS who need laparoscopic assessment of their pelvis or who live too far away from the hospital for the intensive monitoring required during gonadotrophin therapy.[21]

Commonly employed methods for LOS include monopolar electrocautery (diathermy) and laser. There does not appear to be a difference in outcomes between the two modalities [25]. Most authors use between four and ten punctures; however, more punctures have been associated with premature ovarian failure (Malkawi et al., 2003).

LOS is an alternative to gonadotrophin therapy for CC-resistant anovulatory PCOS. The treatment is best suited to those for whom frequent ultrasound monitoring is impractical and in PCOS patients where aimis to achieve unifollicular ovulation with no risk of OHSS or high-order multiples. As in all surgical procedures, an important issue of successful outcome is the expertise of the surgeon. The risks of surgery are minimal and include the risk of laparoscopy, adhesion formation and destruction of normal ovarian tissue. [26] There are no data regarding repeated application of LOS and such use should not be encouraged. In >50% of LOS-treated women, adjuvant therapy will be required. In these women, the addition of CC can be considered after 12 weeks if no ovulation is detected. The addition of FSH should be considered after six months [25].

Assisted reproduction techniques: IVF

After failure of weight reduction, anti-estrogen therapy or LOS and induction of ovulation with exogenous gonadotrophin therapy, ovarian stimulation and IVF may be considered.By utilizing IVF with single-embryo transfer, the risk of multiple pregnancies is markedly reduced.[27] In women with PCOS who do have associated pathologies, IVF is indicated, such as in case of tubal damage, severe endometriosis, preimplantation genetic diagnosis and male factor infertility.

Regarding the probability of pregnancy, the clinical pregnancy rate per started cycle was similar (_e"35%) between PCOS and non-PCOS patients. The same was true for pregnancy rates per oocyte retrieval and embryo transfer (ET). This observation suggests that implantation is not compromised in PCOS.[28]

There is some evidence that the adjuvant use of metformin may enhance ongoing pregnancy rates and reduce the incidence of OHSS.[28] IVF is a reasonable option, because the number of multiple pregnancies can be kept to a minimum by transferring small numbers of embryos.

ART: Ovulation induction and homologous artificial insemination

Since subfertility in women with PCOS is mainly due to anovulation, induction of ovulation is the main treatment for women with PCOS. In women with PCOS who failed to conceive despite successful induction of ovulation, IUI may also be considered. Induction of ovulation in combination with IUI is indicated in women with PCOS and an associated male factor and may be proposed in women with PCOS, who failed to conceive despite successful induction of ovulation.[29]

To summarise, before any intervention is initiated, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women. Overall, ovulation induction (representing the CC, gonadotrophin paradigm) is reported to be highly effective with a cumulative singleton live birth rate of 72%.

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