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Review Article

Ovulation induction in polycystic ovarian syndrome - basics for gynecologist

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is the most common problem related to infertility among women. This review looked into the evidence and options available for ovulation induction. The management protocol and their respective efficacy was looked into during the write up of the review. Weight reduction, along with metformin therapy are the initial and efficient way to regain ovulation among obese female. This should be complemented by use of first line medicine like aromatase inhibitors and selective estrogen receptor modulators. The first line is effective in significant proportion of female to induce ovulation and increase live birth rate. However, for those not responding should initially undergo the use of gonadotropins and ovarian drilling. Finally, controlled ovarian stimulation and in vitro fertilization should be considered as it is an invasive, expensive and there are risks of ovarian hyperstimulation and multiple gestation.

Keywords: PCOS, Ovulation induction, Gonadotropins, Live birth

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder affecting women of adolescent age, child bearing age group and also postmenopausal age. It is an important cause of ovulatory dysfunction, menstrual irregularity and androgen excess. It affects about 20% of the adolescent and adult female in Indian subcontinent.^{1,2} PCOS is one of the most common cause of anovulation and infertility, it accounts to about 25 to 30% of the cause of infertility in women.³

The relationship between hyperandrogenism and anovulation is complex. In PCOS women there is an increased pulsatility of gonadotropin-releasing hormone (GnRH), resulting in increased release of luteinizing hormone (LH) and an elevated LH/follicle-stimulating hormone (FSH) ratio.⁴ Because of low level of FSH level, follicles growth is arrested at different stage of maturation (2-10 mm diameter). This results in decreased estrogen and increased inhibin production. Elevated LH

causes more androgen production from theca cells or from stroma. FSH induces aromatization of this androgen to estrogen, resulting in androgenic follicular microenvironment. This all process ultimately results in anovulation.⁵ Several methods are used for effective ovulation which includes lifestyle modification directed towards weight loss, clomiphene citrate, metformin, gonadotropins, ovarian drilling, in vitro fertilization, etc. This review will discuss on the treatment modalities available for induction in PCOS.

METHODOLOGY

A literature searches in PubMed, Google Scholar and Cochrane Database using the keywords and MeSH term polycystic ovarian syndrome, ovulation, infertility, obesity, insulin sensitizer, aromatase inhibitor, letrozole, metformin, gonadotropins, ovarian drilling, in vitro fertilization, estrogen receptor modulators was done. Important and relevant information was extracted to give completeness to this review article.

DISCUSSION

There are few important steps to be undertaken before initiating ovulation induction, which includes history and evaluation of both the couple. Specifically, history regarding regular sexual intercourse, use of any contraceptive measures, discussion on the expenditure of the therapy, evaluation of the couple stress and state of mind, their availability of time and their dedication towards therapy and regular follow up should be done. Similarly, evaluation of tubal patency by hysterosalpingography (HSG) or laparoscopy with chromotubation along with semen analysis are mandatory before starting the medical therapy.⁶ Different modalities of ovulation induction in PCOS will be discussed in a sequential manner.

Weight reduction and life style modification

Weight reduction along with lifestyle modification should be the first step in the management of overweight PCOS, because this has been proven to be effective in restoring ovulatory cycles and achieving pregnancy. This has also shown to improve the efficacy of medical therapies and improve the likelihood of pregnancy with live birth. Preconception lifestyle modification, like cutting of calories with meal replacements, exercise, use of oral weight loss medication like orlistat or sibutramine has shown to increase the ovulatory rate. After weight reduction of 7% in a clomiphene induced cycle, cumulative ovulation could rise by 60%, with rise in live birth rates by 26%.⁷ In addition six weeks of structured exercise training and hypocaloric diet would increase the likelihood of ovulation with clomiphene in clomiphene resistant overweight PCOS by a factor of 4.⁸

Regular exercise and weight loss increase insulin sensitivity and improves metabolic parameters. Excessive caffeine intake, alcohol consumption, and smoking should also be discouraged.⁹ Maintaining weight and diet also decrease maternal complications like gestational hypertension, gestational diabetes mellitus, thromboembolism, and wound infection.¹⁰ Lifestyle modifications is also a modifiable risk factor for long term cardiovascular disease and type 2 diabetes among women with PCOS.

Insulin sensitizing agents (metformin)

PCOS is a state of insulin resistance and hyperinsulinemia.¹¹ Metformin is a biguanide and it acts by inhibiting hepatic glucose production and increasing peripheral glucose intake. Its role as an insulin sensitizer has led to its widespread use in PCOS in conjunction with other ovulation inducing agents.¹² However, there are very limited use of other insulin sensitizing agents like D-chiroinositol, rosiglitazone or pioglitazone, and are not discussed here. Metformin alone could significantly increase the ovulation rate vs placebo (23% vs 13%), while it does not significantly increase the pregnancy or

live birth rate.^{13,14} Similarly, a recent Cochrane review suggests that metformin may improve live birth rates compared with placebo (odds ratio (OR) 1.59, 95% CI 1.00 to 2.51). Although, there were more gastrointestinal side effects (OR 4.76, 95% CI 3.06 to 7.41), metformin had higher rates of clinical pregnancy (OR 1.93, 95% CI 1.42 to 2.64), ovulation (OR 2.55, 95% CI 1.81 to 3.59) and improved menstrual frequency (OR 1.72, 95% CI 1.14 to 2.61). There was no clear evidence of a difference in miscarriage rates (OR 1.08, 95% CI 0.50 to 2.35).¹⁵ Metformin plus clomiphene citrate had higher rate of clinical pregnancy than clomiphene citrate alone (OR 1.59, 95% CI 1.27 to 1.99) and ovulation was also higher (OR 1.57, 95% CI 1.28 to 1.92). The anticipated clinical pregnancy rate and live birth rate could be projected to 338 vs 243 and 295 vs 257 per 1000 women.

Hence, it is advisable to use metformin and clomiphene combined irrespective of obesity status among PCOS women.¹⁵ The advised starting dosage of metformin should be 500 mg daily with main meal, for 1–2 weeks which should be increased weekly or biweekly by 500 mg a day until a maximum dose of 2000-2500 mg/day is reached depending on the clinical benefit and side effects. If the dose increase results in worsening of the side effects, the current dose can be maintained for 2–4 weeks until tolerated. To lessen the side effects slow-release metformin can be used.¹⁶

Selective estrogen receptor modulators–clomiphene citrate

Clomiphene acts by binding to estrogen receptors and thus has an antiestrogenic effect both on hypothalamus and pituitary. This results in increase in FSH which in turn causes follicular development, increase in estradiol is followed by endogenous LH surge. High FSH level in early follicular phase may result in recruitment of more than one follicle. Clomiphene is an effective first line medicine for ovulation induction, however there are risks of multiple pregnancy.¹⁷

Compared to placebo clomiphene can increase the pregnancy rate (OR 5.8, 95% CI:1.6–21.5), with up to an 11% risk of multiple pregnancy.^{18,19} Hence, regular USG to evaluate the ovarian response should be monitored. The starting dose of clomiphene is 50 mg/day from the 2nd day of the menstrual period and should be given for 5 days, the dose should be increased to 100mg/day if there is no ovulation for 2 cycles with the previous doses. Despite of a dosage of 100 mg/day if the cycles remain anovulatory, the cases is levelled as clomiphene resistant and discontinuation of clomiphene therapy should be considered.²⁰ Following, clomiphene therapy 60 to 85% of PCOS undergoes ovulation, while only 50% of them conceive.^{21,22} The thinning of endometrium secondary to antiestrogenic usually prevents conception despite ovulation. Alternatives for ovulation induction should be considered if periovulatory endometrium remains persistently thin. Along with multiple gestations,

vasomotor hot flushes, blurring of vision and increased risk of borderline ovarian tumor are potential side effects with clomiphene citrate.^{23,24}

Aromatase inhibitors – letrozole

AIs inhibits the cytochrome P450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex and down-regulate the production of estrogen.²⁵ The negative feedback loop of oestrogen in the hypothalamus is inhibited, resulting in stronger gonadotropin-releasing hormone (GnRH) pulses. This in turn stimulates the pituitary gland to produce more FSH, which induces development of follicles in the ovaries. In contrast to Clomiphene, the central feedback mechanism remains intact and as the dominant follicle grows and oestrogen levels rise, normal negative feedback occurs centrally suppressing FSH and hence usually resulting in single dominant follicle.²⁶

In a Cochrane database review, letrozole compared to clomiphene citrate (CC) with or without adjuncts has higher birth rate (OR 1.68, 95% CI 1.42 to 1.99). However ovarian hyperstimulation syndrome rates are similar with letrozole or clomiphene citrate. There is evidence for a higher pregnancy rate in favour of letrozole (OR 1.56, 95% CI 1.37 to 1.78). There is little difference between letrozole groups in the rate of miscarriage by pregnancy (19% versus 20%, OR 0.94, 95% CI 0.70 to 1.26) and multiple pregnancy rate (1.3% versus 1.7%; OR 0.69, 95% CI=0.41 to 1.16).²⁷

Letrozole is usually administered from the 3rd day of the menstrual cycle for total of 5 days. To start with dosage is usually begun at 2.5 mg daily and the basis of development of adequacy of follicular size and endometrial thickness, as deemed necessary the dose could be increased to 5 mg and subsequently to 7.5 mg daily in the consecutive cycle on the basis of individual response.²⁸ Letrozole as a side effects could cause fatigue and dizziness. But importantly concerns on congenital anomalies in fetus with letrozole therapy were raised. However, in recent studies it has been found that there are no significant differences in congenital anomalies between letrozole or clomiphene groups.^{29,30} Conclusively, letrozole could safely be used as a second line therapy for ovulation among PCOS women.

Gonadotropins

Gonadotropins are second line therapy for those who have failed to respond to Clomiphene therapy. This method of inducing ovulation is based on the concept that administration of FSH will results in follicular growth and development and FSH above threshold level for sufficient duration would generate a limited number of developing follicles. There are different approaches towards administration of gonadotropins. The preferred one is the step-up protocol. The FSH dosage is started at 37.5-75 IU/day from, if follicle development is not

observed on USG after a week, dose is increased by 50%. Once follicular growth is observed same dose is maintained until follicular selection is achieved.³¹ In step-down protocol the higher dose 150 IU/day is given until there is follicular development in USG and subsequent stepwise reduction is done.³² However, step up is safer and easily instrumented in comparison to the later protocol.³³ The consensus on fertility related to PCOS has also recommended the use of gonadotropins at initial dose of 37.5-50 IU/day to reduce the risk of ovarian hyperstimulation syndrome (OHSS).³⁴ The low dose regimen has a good efficacy with ovulation rate of 70%, pregnancy rate of 20% and multiple live birth rate of <6% and OHSS rate of <1%.^{33,35} Short protocol with GnRH antagonist reduces the risk of hyperstimulation but also it interferes with LH surge and hence result in lower rate of pregnancies.³⁶ It is also demonstrated that combine use of metformin along with FSH therapy elicit a lower rate of OHSS.³⁷ Gonadotropins is a complex and expensive method of ovulation induction; it requires a tight monitoring along with risk associated with ovarian hyperstimulation and multiple gestation. Hence, this approach should be reserved as a last resort before proceeding towards invitro fertilization (IVF) technique.

Laparoscopic ovarian drilling (LOD)

Laparoscopic ovarian drilling is an invasive procedure reserved for its use when there is poor response of ovulation with medical management in women with PCOS. In this procedure by using laparoscopic ovarian cautery or diathermy multiple perforations are done in the ovarian surface and stroma. This destroy ovarian androgen-producing tissue and reduce the peripheral conversion of androgens to estrogen, which results in fall of LH and rise of FSH and increases the chances of ovulation.³⁸ LOD could increase the ovulation rate of ovulation induction therapy from 39% to 77% and pregnancy rate from 33% to 47%.³⁹ Recent Cochrane review data suggests that LOD have a decreased live birth when compared to medical ovulation alone (OR 0.71, 95% CI 0.54 to 0.92).

The evidence suggests that chance of medical ovulation alone is 42% while LOD could have ovulation rate between 28% and 40%. Medical ovulation would have a risk of multiple pregnancy of 5%, LOD decreases the risk of multiple pregnancy with medical ovulation between 0.9% and 3.4%. However, there was little or no difference with miscarriage frequency. LOD however may reduce OHSS (OR 0.25, 95% CI 0.07-0.91). There are limited study to suggest need of bilateral LOD versus unilateral LOD.⁴⁰ Hence, LOD is an invasive option that could be provided to the women who are resistant to first line therapy of medical ovulation.

In vitro fertilization

IVF is an invasive option left for PCOS with failure of gonadotropin therapy or in combination with tube related

issues of infertility, or have significantly reduced number or quality of sperms. In IVF, for multi-follicular development firstly, gonadotropins are administered after which oocyte retrieval is carried out, once embryos are generated, they are transferred to the uterus. Pregnancy rate can approach 40% to 50% per cycle with IVF.⁴¹ However, the risk of OHSS is significantly increased, even with the use of GnRH antagonist protocols. Time and cost related issues should always be discussed with the couple opting for IVF before enrolling for the therapy.

CONCLUSION

PCOS is the common problem in women of reproductive age group related to infertility. However, many time-tested options are available. Base on the availability, individual metabolic status, complexity and adverse effects of treatment options, preferences should be made. All overweight women should undergo weight reduction protocol; metformin use has shown to be beneficial even when opting for inducing ovulation with other available options. First line for ovulation induction is either letrozole or clomiphene citrate. For those resistant to first line therapy gonadotropins along with ovarian drilling could be considered. Finally, for those not ovulating or conceiving or having issues related to fallopian tubes or semen should undergo IVF.

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