



# “What to Do”: Infertility in Polycystic Ovarian Syndrome



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## Abstract

Polycystic ovarian syndrome is a multifarious syndrome that affects approximately 5-10% of women in reproductive age group. Infertility is one of the most common clinical manifestations of this. The main reasons attributable to infertility are ovulatory dysfunction and negative effects of hyperandrogenism on the same. Treatment of infertility thus includes lifestyle modification, clomiphene citrate, metformin, gonadotropins, ovarian drilling and IVF as the last resort. The purpose of this mini review is to update the knowledge of the clinicians for the better and optimal management of the patients.

## Polycystic Ovarian Syndrome and Clinical Manifestation

Polycystic ovarian syndrome (PCOS) affects approximately 5-10% of women in reproductive age group. [1] Diagnosis of PCOS is based on Rotterdam's criteria 2003, according to which two of the three criteria should be fulfilled and these include oligo-ovulation or an ovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovaries on ultrasound characterized by more than 12 small antral follicles per ovary excluding conditions like Cushing's syndrome, congenital adrenal hyperplasia and androgen secreting tumours [2]. The reproductive abnormality in patients with this syndrome is multitudinous. Menstrual abnormality is due to infrequent or absent ovulation, more so seen in obese patients. Majority of these patients also have abnormal gonadotropins secretory dynamics. Follicular development is also abnormal owing to the arrest of development of ovarian follicles at late antral stage and abnormal endocrine milieu i.e. low follicular fluid estradiol levels and high androgen levels. At least 50% of women with PCOS are obese and most women have hyperinsulinemia and insulin resistant leading directly and indirectly to hyperandrogenism, all these factors thus hampering fertility [3]. In a study, it was found that the prevalence of metabolic syndrome in women with PCOS was 47% as compared to 4% in age matched control with normal menstrual cycle and no hirsutism [4]. In another study of one hundred twenty-two women with PCOS, 35% had impaired glucose tolerance and 10% had type 2 diabetes mellitus by the age of 40 years [5].

The pregnancy complications in this group of women are also high, as can be deciphered from a meta analysis of 27 studies including 4982 patients. Odds ratio of developing gestational diabetes mellitus, pregnancy induced hypertension, pre eclampsia and

preterm birth were 3.4, 3.4, 2.2 and 1.9 respectively, as compared to general obstetric population. Also, rates of early pregnancy loss are on a higher side [6].

## Ovulation Induction In PCOS

The options available to achieve ovulation in patients with polycystic ovarian syndrome and thus pregnancy can be non-pharmacological or pharmacological.

## Non-Pharmacological Methods

Weight loss with the help of exercise and diet and lifestyle modification is regarded as the first line of management of infertility in this group of women. It is studied that even 5-10% of weight loss helps in restoring ovulatory function and thus achieving pregnancy [7].

## Pharmacological Methods

Clomiphene citrate is a selective estrogen receptor modulator and is used as a first line ovulation induction agent for almost four decades now. It acts by binding to estrogen receptors in hypothalamus and pituitary and this leads to increased endogenous follicle stimulating hormone levels and thus leading to follicle development and ovulation in 60-85% of patients [8]. On the contrary, its antiestrogenic effect on the endometrium leads to only half of the patients conceiving. In one of the studies, no pregnancy occurred when endometrium is less than 6mm at midcycle, but other studies didn't find any such correlation [9]. The dose starts from 50mg per day for 5 days starting between day 2 and 5 of menstrual cycle and can be increased to maximum of 250mg per day for 5 days and

maximum of 6 ovulatory cycles. Side effects of this drug include multiple pregnancy, hot flushes and rarely visual symptoms. Next drug in line is metformin, a biguanide insulin sensitizing agent that acts by increasing peripheral glucose uptake and inhibiting hepatic glucose production. In a study by Siebert et al, six trials were examined in which metformin was randomized with either placebo or clomiphene citrate in clomiphene resistant patients and found a statistically significant improvement in ovulation with combination therapy (OR 6.82) [10]. Dose of the drug starts with 250mg to 500mg per day to maximum of 750mg three times a day and have side effects like nausea, cramps, bloating and diarrhoea. Gonadotropins are used when these patients fail to conceive with oral ovulation induction medication as second line therapy. These are administered as daily injections combined with ultrasound monitoring and serum estradiol levels to ensure unifollicular growth and development with pregnancy rates of 20-25% per cycle [11]. There exists a high risk of multiple pregnancy, ovarian hyper stimulation syndrome and overall the cost of treatment entails burden on the patient. Laparoscopic ovarian drilling (LOD) may be considered in patient with PCOS and especially when there exists an indication for laparoscopy but taking into consideration existing surgical risks. This is particularly helpful in patients with clomiphene resistant PCOS, with ovulation rate comparable to that with gonadotropins after LOD. Aromatase inhibitors like letrozole, anastrozole act by inhibiting the conversion of testosterone and androstenedione to estradiol and estrone respectively, thus inhibiting estrogen negative feedback on the hypothalamic pituitary axis. This helps in increasing gonadotropin secretion and thus ovarian follicular growth and development. In a study presented in ASRM 2005, it was found that letrozole use as ovulation induction drug is associated with increased risk of congenital malformations [12]. In later years, a study done by Tulandi et al evaluated 911 newborns from letrozole and clomiphene citrate pregnancy and found that the incidence of congenital malformations was 2.4% in letrozole group compared to 4.8% in CC group [13]. In patients with PCOS who fail to respond to above mentioned treatment or have other indications for advanced reproductive technologies, IVF is a rescue management option. Pregnancy rate per cycle is expected to be around 40-50% and similar to the patients without PCOS [11].

## Conclusion

The most common and worrisome clinical manifestation of PCOS is infertility. The main reason behind this is oligo-ovulation or anovulation and other factors like hyperandrogenism, hyperinsulinemia and obesity. Lifestyle modification, weight reduction and exercise form the first line of management for these group of patients. The next in line is ovulation induction drugs like clomiphene citrate and metformin which helps in decreasing insulin resistance, both together improving ovulation and pregnancy rate.

Next in line are gonadotropins when oral ovulation induction fails. LOD is an option in patients with clomiphene resistant PCOS and with other indications for laparoscopy and finally IVF when all previous treatment fails. But, the treatment has to be optimized based on patient's age, duration of infertility and other factors hampering her fertility. So, important is what to do in patients with infertility having this heterogeneous endocrine condition..

## References

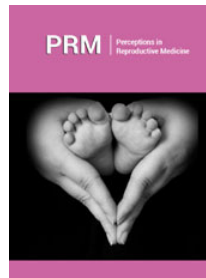
1. Knonchenhauer ES, Key TJ, Kahsar MM, Waggoner W, Boots LR, et al. (1998) Prevalence of the polycystic ovary syndrome in unselected black and white women of the south eastern United States: a prospective study. *J Clin Endocrinol Metab* 83(9): 3078-3082.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 81(1): 19-25.
3. Dunaif A, Segal KR, Futterweit W, Dobrjansky A (1989) Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 38(9): 1165-1174.
4. Dokras A, Bochner M, Hollinrake E, Markham S, Vanvoorhis B, et al. (2005) Screening women with polycystic ovary syndrome for metabolic syndrome. *Obstet Gynecol* 106(1): 131-137.
5. Ehrmann DA, Branes RB, Rosenfield RL, Cavaghan MK, Imperial J, et al. (1999) Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 22(1): 141-146.
6. Qin JZ, Pang LH, Li MJ, Fan XJ, Huang RD, et al. (2013) Obstetric complications in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Reprod Biol Endocrinol* 11: 56.
7. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, et al. (2004) Improving reproductive performance in overweight/obese women with effective weight management. *Hum Reprod Update* 10(3): 267-280.
8. Neveu N, Granger L, Michel P, Lavoie HB (2007) Comparison of clomiphene citrate, metformin, or the combination of both for first line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome *Fertil Steril* 87(1): 113-120.
9. Dickey RP, Olar TT, Taylor SN, Cuore DN, Matulich EM (1993) Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropins *Fertil Steril* 59: 756-760.
10. Siebert TI, Kruger TF, Steyn DW, Nosarka S (2006) Is the addition of metformin efficacious in the treatment of clomiphene citrate resistant patients with polycystic ovary syndrome? A structured literature reviews *Fertil Steril* 86(5): 1432-1437.
11. Guzick D (2007) Ovulation induction management of PCOS. *Clin Obstet Gynecol* 50(1): 255-267.
12. (2005) Health Canada Endorsed Important Safety Information on Femara (letrozole). Novartis Canada Inc, Canada.
13. Tulandi T, Martin J, AL-Fadhli R, Kabli N, Forman R, et al. (2006) Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate *Fertil Steril* 85(6):1761-1765.



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