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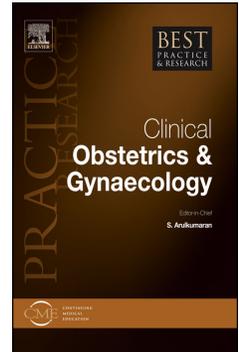
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Ovulation Induction in Polycystic Ovary Syndrome: Current Options

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ABSTRACT

There are a variety of effective treatment options to induce ovulation in women with polycystic ovary syndrome (PCOS). The most effective treatments are primarily reproductive and target the hypothalamic-pituitary-ovarian (HPO) axis. Letrozole, an aromatase inhibitor, is headed towards replacing clomiphene, a selective estrogen receptor modulator, as the first choice option. Metabolic treatments likely work indirectly through the HPO axis. Many metabolic treatments have shown initial promise and later failed (troglitazone or d-chiro-inositol) or disappointed (metformin), further study is needed of newer agents to treat type 2 diabetes. Weight loss interventions, both lifestyle related, through obesity drugs, or through bariatric surgery have shown mixed results on pregnancy outcomes. With both reproductive and metabolic treatments, combination therapies (such as metformin and clomiphene together) may offer greater benefit to distinct subgroups of patients.

INTRODUCTION

This chapter will review current strategies for ovulation induction in women with PCOS focusing primarily on clinical aspects, identifying risk benefit ratios, and areas of uncertainty. While it will acknowledge summary meta-analyses of treatment options where relevant, there will also be some detailed discussion of individual clinical trials and pearls obtained from the study. Treatments can primarily be divided into those that directly effect the reproductive axis, i.e. the hypothalamic-pituitary-ovarian axis and those that act metabolic factors, and thus likely indirectly perturb the hypothalamic-pituitary-ovarian axis. Combination therapies where we have existing data will also be discussed. The primary treatments to be discussed are found in Table 1.

REPRODUCTIVE APPROACHES TO OVULATION INDUCTION

Aromatase Inhibitors

Aromatase inhibitors are thought to induce ovulation in women with PCOS through reduction in inappropriate feedback of weak circulating estrogens, such as estrone, which correspondingly results in increased FSH secretion and follicular development. Many of these weak estrogens may result from peripheral conversion of androgens into estrogens by other tissues. Given the preponderance of adipose tissue in women with obesity, these drugs may offer a unique benefit in this subpopulation, though the data are mixed about whether obesity interacts with letrozole, the most studied aromatase inhibitor in ovulation induction to date. Other purported benefits are a lower rate of multifollicular recruitment and ovulation, a lesser anti-estrogenic effect on the endometrium than selective estrogen receptor modulators, and its own unique safety profile.^{1,2} The most

common side effects with letrozole are headache and cramps. Compared to clomiphene, women on letrozole have fewer hot flashes, but more fatigue and dizziness. One of the initial concerns about letrozole, based on unpublished epidemiologic data, was an increased risk of congenital anomalies. Observational studies have supported that rates are similar to those after clomiphene,³ further two large prospective randomized trials that studied letrozole in women with PCOS⁴ and women with unexplained infertility⁵, support that cumulative rates of teratogenicity with letrozole are less than 5%, comparable to rates with clomiphene, and less than or equal to expected rates based on population reports of birth defects after ovulation induction or in vitro fertilization in an infertile population.⁶ The half life of letrozole is around 2 days, substantially shorter than clomiphene. Despite these reassuring data, letrozole is proscribed in many parts of the world with 'black box' warnings on the product label. This author, before making the recommendation for more studies showing safety, would first request the data showing harm in terms of increased congenital anomalies.

Success rates of letrozole compared to clomiphene, the usual first line ovulation induction therapy in women with PCOS, based on current meta-analyses, suggests that women with PCOS are about 50% more likely to have a live birth with letrozole compared to clomiphene.⁷ The mechanisms behind this improved performance may be related to the lowering of estradiol levels (in comparison to other ovulation induction methods such as clomiphene and gonadotropins) and also a relative increase in luteal progesterone levels, mimicking a more natural implantation environment (Figure 1). The number of ovarian follicles which develop appears comparable to clomiphene. While

there is a slight decrease in the multiple pregnancy rate compared to clomiphene, this is not statistically significant in trials or meta-analyses to date. From a public health perspective, further study of multiple pregnancy rates is necessary.

Anastrozole has also been studied, but performed markedly inferiorly to clomiphene and development of the drug by the sponsoring pharmaceutical company was stopped.⁸ Single dose therapy of anastrozole was also relatively ineffective.⁹

Selective Estrogen Receptor Modulators

Clomiphene citrate is the most commonly used selective estrogen receptor modulator (SERM) in ovulation induction in women with PCOS, although tamoxifen has also been studied for this indication. Currently the choice of first line treatment agent for ovulation induction in women with PCOS is debatable between letrozole and clomiphene, though some voices in the wilderness argue for low dose gonadotropin therapy.¹⁰ Interestingly as with aromatase inhibitors, SERMs were originally developed for the treatment of hormone dependent breast cancer. SERMs are thought to have a related, but unique mechanism of action as letrozole. Specifically they are thought to function as estrogen receptor antagonists in the hypothalamus and stimulate GnRH and subsequent FSH secretion. They may also have similar effects elsewhere in the body, for instance, they may antagonize estrogen stimulated endometrial development, thus inhibiting implantation while favoring ovulation. Overall, however clomiphene has an estrogenic effect as indicated by the significant increases in circulating sex hormone binding globulin

levels after even short exposures (i.e. 5 days). The increase in SHBG is much less with aromatase inhibitors. The metabolism of clomiphene is complex as it is a racemic mixture of two isomers (zu- and en-clomiphene which may have varying effects), and has a long half life (5-7 days) such that metabolites may accumulate over time with carry-over effects in consecutive cycles.¹¹

Hot flashes are noted as a particularly annoying side effect by patients. Further there is a theoretical concern about a sudden development of visual symptoms due to potential pituitary enlargement and this can be a reason for treatment discontinuation though clinically it is often to determine the source of such symptoms without intensive and expensive brain imaging. Multiple pregnancy rates are in the range of 5-8% and most are twins, though case reports have also documented high order multiple pregnancies after clomiphene use.

Clinical Use of Anti-Estrogens and SERMS

Letrozole has been given in clinical studies in a similar fashion to the better established clomiphene. Both are given in the early follicular phase, or more correctly stated, the constant follicular phase of anovulatory women with PCOS. The starting dose for letrozole is 2.5 mg a day for 5 days, for clomiphene it is 50 mg a day for 5 days. Many groups will perform a baseline ultrasound with serum progesterone screening to rule out periodic and unexpected ovulation. At a minimum, it is prudent to perform a urine pregnancy test to rule out potential

exposure of an early pregnancy to the medication before any dose is given. This advice is practical for all ovulation induction methods in women with PCOS.

It is debatable whether an induced withdrawal bleed is necessary prior to ovulation induction or between anovulatory cycles if a patient is non-responsive to medication (i.e. letrozole or clomiphene resistant).¹² My current practice is to avoid it, unless there is ultrasound evidence of a potential abnormality. There are limited data to suggest that follicular phase monitoring and triggering of ovulation with hCG is superior to no monitoring and timed intercourse. It is expedient to monitor for ovulation in the follicular phase to allow for rapid advancement of starting doses if there is no ovulation or follicular development using the so-called stair step protocol with dose increases every 2-3 weeks without follicular development.¹³ The dose of letrozole is increased by 2.5 mg a day up to a maximum daily dose of 7.5 mg for 5 days, and for clomiphene the dose is increased by 50 mg a day up to a maximum daily dose of 150 mg a day. Higher daily doses of clomiphene have been given with reported success or longer duration of dosing beyond 5 days.¹⁴ Similar studies with letrozole have not been as widely reported.

Many issues with these two drugs still need addressed. The ideal number of cycles has not been established, but longer studies have shown that time does not diminish the per cycle pregnancy rates with with clomiphene over 6 cycles^{15,16} or letrozole over 5 cycles⁴. This, if a patient is ovulating, a longer course may be indicated if other factors do not lead to more advanced therapies. Also unknown is whether the

sequential use is beneficial (and which sequence!). , i.e. if a patient ovulates but fails to conceive after letrozole, should she continue with clomiphene or move on to gonadotropins.

Gonadotropins

Recombinant or menopausal gonadotropins have been used traditionally as second line therapy for ovulation induction, though head to head studies suggest a higher pregnancy rate than clomiphene.¹⁰ FSH preparations are thought to offer the best physiologic approach, given the relative elevation of circulating LH to FSH in many women with PCOS. Because women with PCOS are at increased risk for the adverse events of gonadotropin use, such as ovarian hyperstimulation syndrome and multiple pregnancy, because of their relative youth compared to other infertility patients and their high number of antral follicles (and corresponding AMH levels), low dose regimens should be used. Such low dose regimens often begin at low daily doses of 37.5-75 Units a day with modest increases as needed only every 10-14 days, and with over-response dose reductions. Such regimens in experienced hands produces excellent pregnancy outcomes with a low multiple pregnancy rate.¹⁷ Often the first cycle

Pulsatile GnRH

Pulsatile GnRH has been given to women with PCOS and successfully results in ovulation and pregnancy. Limiting factors have been the unwieldiness of the pump compared to a daily shot or pill, the varying availability of GnRH for infusion, and

the need, with increasing concern about infection, to avoid sharing the pump among patients as was commonly done when this form of therapy was first developed.

There is current interest in this technology for other ovulatory disorders, so there may be renewed use of this therapy in the future.

METABOLIC APPROACHES TO OVULATION INDUCTION

Metformin

Metformin is a biguanide approved for the treatment of type 2 diabetes as a hypoglycemic agent. It is estimated that 10-15% of its efficacy in type 2 diabetes is due to peripheral improvement in insulin sensitivity, primarily in skeletal muscle. Thus, unlike the thiazolidinediones, metformin is not primarily an insulin sensitizing drug, though it is often labeled as such in the treatment of women with PCOS. Groundbreaking studies over 20 years ago established that metformin is associated with reductions in circulating androgens, likely through direct ovarian effects, and improved ovulation rates compared to placebo.^{1,18,19} Meta-analysis has also established these qualities as well as increases in pregnancy rates compared to placebo.²⁰

Unfortunately despite the hype surrounding metformin as an infertility drug, head to head studies, comparing metformin to clomiphene have consistently shown that pregnancy and live birth rates are significantly lower with metformin alone.²⁰ Even when differences in the ovulation rate are accounted for, the use of

clomiphene is associated with a significantly higher chance for pregnancy than metformin alone, roughly a two fold increase (Figure 2).

There are many myths about metformin. One is that there is a prolonged period of treatment required before it becomes efficacious. This is not supported by the effects in type 2 diabetes where effects are noted within days, further studies do not support there is a time related increase in either ovulation or pregnancy alone. A second myth is that there are differences in ovulation rates based on the type of metformin with immediate release better than the extended release form. No study in PCO has specifically addressed the difference between the two preparations, but studies in type 2 diabetes have established equal efficacy on glyceimic parameters. The ideal dose in PCOS is debated though higher doses may have greater weight loss.²¹ Most studies have used a total dose of 1500 to 2550 gms a day given in divided doses (BID or TID).

Metformin may be most useful as an adjuvant ovulation induction therapy. In a Finnish multi-center trial, pregnancy rates increased when adjuvant therapy was added after 3 mos and benefit was greatest in the obese subgroup with PCOS.²² Post hoc studies of metformin and clomiphene supported a greater benefit in obese women on live birth rate compared to the thinner comparison group.¹⁶ Metformin does not appear to effect the miscarriage rate or to lower perinatal complication rates such as pre-eclampsia or gestational diabetes in women with PCOS though

studies are still ongoing.²³ Therefore, there are few data to support continuing metformin throughout pregnancy.

Thiazolidinediones

Thiazolidinediones are approved for type 2 diabetes and work as peripheral insulin sensitizers. The initial drug of this family, troglitazone, was studied extensively in PCOS but was removed from the market due to hepatotoxicity. Other safety concerns have haunted rosiglitazone (cardiovascular morbidity) and pioglitazone (bladder cancer). Their use in type 2 diabetes has been curtailed. Given the side effect of weight gain that frequently accompanies the drug as well as the relatively unknown pregnancy effects, these remain a class of drugs with little use in ovulation induction for women with PCOS.

Inositol

Interest in inositol as a treatment for PCOS was stirred by a randomized controlled trial that showed an isomer of inositol (d-Chiro-inositol) markedly improved insulin sensitivity, lowered testosterone and improved ovulation rates.²⁴ However phase II studies of this compound (developed as a pharmaceutical) failed to show a similar benefit in multi-center, larger trials and development of the drug was cancelled and results of the Phase II trials were never published. Inositol is a sugar alcohol with multiple stereoisomers, and combinations of these stereoisomers are available as supplements in the U.S. and other countries. Interest for further use in PCOS drifted to one of the isomers, myo-inositol which can serve as a precursor to

second messengers (involved in glucose action) and phospholipids in human cells. The two most commonly studied isomers, myo and chiro may have opposing and tissue specific action. Combinations of myo- and chiro-inositol have been used and a recent international consensus conference recommended using myo:chiro inositol in PCOS in a 40:1 ratio.²⁵

WEIGHT LOSS

Lifestyle

Experts have recommended weight loss prior to ovulation induction with PCOS, but this is not evidence-based. Evidence from both observational trials and randomized trials supports that modest weight loss may increase the spontaneous pregnancy rate^{26,27} and the pregnancy rate after ovulation induction with clomiphene²⁸. Another post hoc study that compared immediate treatment with clomiphene citrate versus delayed treatment found a significant improved 2.5 fold increased live birth rate with weight loss prior to ovulation induction.²⁹ However a large pragmatic trial of infertile obese women in the Netherlands found that weight loss (in a 6 mos lifestyle program) was associated with a lower live birth rate over a two year period compared to immediate treatment. Further subgroup analysis showed no live birth benefit in women with anovulatory infertility.³⁰ These conflicting data make clear clinical recommendations difficult until we have further studies or further explanations for the disparate studies.

Obesity Drugs

Although some groups including ours have studied the use of weight loss drugs to achieve weight loss prior to infertility treatment in obese women with PCOS, there are still multiple concerns about potential fetal effects. Some drugs now approved for the treatment of obesity have known teratogenic potential (such as topiramate which is combined with phentermine). Newer obesity drugs such as lorcaserin are scheduled drugs (by the U.S. FDA) with unknown pregnancy effects in humans. Thus further studies are needed until they can be used routinely. A gastric lipase inhibitor, orlistat, is available over the counter in the U.S. and is likely relatively safe, however vitamin supplementation should be done concurrently given the effects of decreased fat absorption of fat soluble vitamins, such as vitamin D.

Bariatric Surgery

Bariatric surgery results in the greatest proportional weight loss, usually 30-40% after Roux-en-Y gastric bypass. There have been many case series reporting improved pregnancy outcomes in obese women with PCOS. There have been few clinical trials, either prospective or randomized. A Swedish database analysis recently reported that obese women who underwent bariatric surgery had shorter gestations and an increased incidence of SGA babies, although they had fewer LGA babies also compared to obese women who did not.³¹ There was a concerning trend towards increased infant mortality in the bariatric group also. Thus bariatric surgery may have its own unique risk benefit ratio on pregnancy outcomes.

CONCLUSION

There are a variety of effective treatment options to induce ovulation in women with PCOS. Most of these are primarily reproductive and target the hypothalamic-pituitary-ovarian axis. Letrozole is headed towards replacing clomiphene as the first choice option. While many metabolic treatments have shown initial promise and later failed (troglitazone or d-chiro-inositol) or disappointed (metformin), further study is needed of weight loss interventions, both lifestyle related, through obesity drugs, or through bariatric surgery. With both reproductive and metabolic treatments, combination therapies may offer greater benefit to distinct subgroups of patients.

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Figure 1: Comparison in Change from baseline to midluteal phase in serum estradiol and progesterone in women who received clomiphene citrate compared to letrozole. From the Pregnancy in Polycystic Ovary Syndrome II study. ⁴ *P < .05

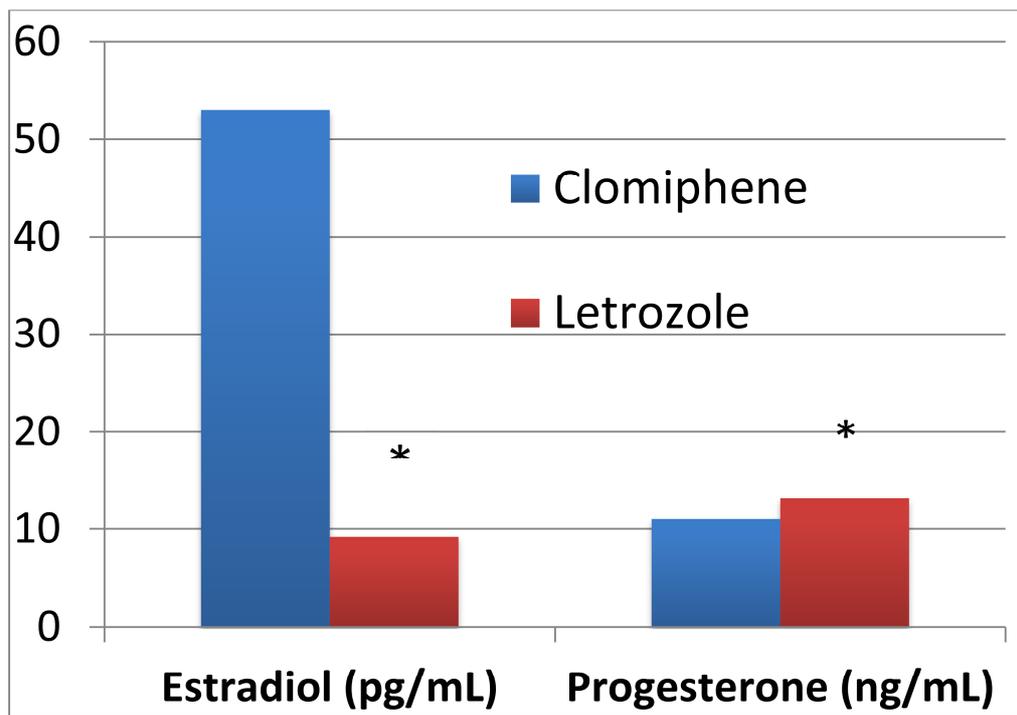


Figure 2: Improved Fecundity per ovulation as noted in the Pregnancy in Polycystic Ovary I study conducted by the Reproductive Medicine Network with Clomiphene alone or in combination with metformin compared to clomiphene alone. CC = Clomiphene, Met = Metformin, Comb= Combination of Clomiphene and Metformin, * $P < .05$ Met vs CC and Met/CC. from Legro et al.¹⁶

