Infertility and PCOS

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introduction

- Ovulatory disorders can be identified in 18 to 25 percent of couples presenting with infertility
- **WHO class 1** – Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea)
- **WHO class 2** – Normogonadotropic normoestrogenic anovulation (almost all women in this category have polycystic ovary syndrome)
- **WHO class 3** – Hypergonadotropic hypoestrogenic anovulation (primary ovarian insufficiency

- A complete history and physical examination
- Laboratory testing – (hCG), (TSH), (PRL) ,(FSH),(AMH?)
- Obese women with PCOS should be screened for **diabetes** and encouraged to lose weight before considering ovulation induction
- **Semen analysis of the partner to identify seminal abnormalities that might contribute to the infertility**

- Hysterosalpingogram if the clinical history suggests **uterine** or **tubal** pathology may also be present and in **women over 35 years of age**

- An endometrial biopsy may be indicated to assess hyperplastic changes in women with chronic anovulation

- A pelvic examination or a pelvic ultrasound to rule out ovarian cysts, especially in patients with known tendency to form functional cysts.

aromatase inhibitor

- Letrozole and anastrozole are triazole (antifungal) derivatives that are potent, reversible, competitive, nonsteroidal aromatase inhibitors

- completely absorbed after oral administration and have a mean terminal half-life of approximately 45 hours (range 30 to 60 hours); clearance is mainly hepatic

- exemestane, a steroidal aromatase inhibitor, has a circulating half-life of approximately nine hours, but the inhibitory effect is potentially much longer because its effect on aromatase is irreversible

- Letrozole, an aromatase inhibitor, blocks the conversion of testosterone and androstenedione to estradiol and estrone

- reducing negative estrogenic feedback at the pituitary and thus increasing follicle-stimulating hormone (FSH) output

- letrozole appears to be free of the adverse effects on endometrial and cervical mucus attributed to clomiphene citrate

- Letrozole is now considered to be **the drug of choice** for ovulation induction in women with PCOS

- the starting dose is 2.5 mg/day, cycle days 3 to 7, following a spontaneous menses or progestin-induced bleed

- If the cycle is ovulatory, but pregnancy has not occurred, the same dose should be used in the next cycle.

- If ovulation does not occur, the dose should be increased to 5 mg/day, cycle days 3 to 7, with a maximal dose of 7.5 mg/day

- Available data suggest that letrozole is superior to clomiphene citrate for the outcome of live birth rates in oligoovulatory women with PCOS

- human studies have not observed teratogenic risks that are greater than those for clomiphene use

- Based on the half-life of letrozole, administration in the early follicular phase should result in clearance of letrozole before implantation takes place.

clomiphene

- Clomiphene citrate has been the most widely used treatment for fertility enhancement for the past 40 year

- selective estrogen receptor modulator (SERM)

- competitive inhibitors of estrogen binding to estrogen receptors (ERs) and have mixed agonist and antagonist activity, depending upon the target tissue

- primary site of clomiphene action is the hypothalamus, where it appears to bind to and deplete hypothalamic ERs, thereby blocking the negative feedback effect of circulating endogenous estradiol

- This results in an increase in hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency and increased serum concentrations of follicle-stimulating hormone (FSH) and (LH).

- clomiphene citrate is now considered to be a **second-line agent** for women with polycystic ovary syndrome (PCOS) as letrozole therapy results in higher birth rates

- Clomiphene citrate therapy for ovulation induction is typically started on the fifth day of a cycle, following either spontaneous or induced bleeding

- The initial dose, empirically, is 50 mg daily for five days; starting with a higher dose does not result in higher pregnancy rates

- If ovulation does not occur in the first cycle of treatment, the dose is increased to 100 mg

- the dose is increased by increments of 50 mg to a maximum daily dose of 150 mg (100 mg is the maximum dose approved by the [FDA], and the [ASRM] suggests that doses >100 mg add little to clinical pregnancy rates)

- Once ovulation is achieved, the same dose should be continued for four to six cycles

- The LH surge occurs from 5 to 12 days after the last day of clomiphene administration.

- The couple is advised to have intercourse every other day for one week beginning five days after the last day of medication

- The response to treatment should be monitored

- Ovulation generally occurs 14 to 26 hours after the detection of the urinary LH surge and almost always within 48 hours

- Royal College of Obstetricians and Gynecologists (RCOG) and the National Institute for Health and Clinical Excellence (NICE), suggest serial transvaginal ultrasound to monitor the number and size of developing follicles and to time hCG administration if necessary

- Induction of ovulation by clomiphene increases the probability of multifetal pregnancy:
- twins have been reported in 6.9 to 9 percent of pregnancies
- triplets in 0.3 to 0.5 percent
- quadruplets in 0.3 percent
- quintuplets in 0.13 percent

- risk may be reduced by ultrasound monitoring and withholding human chorionic gonadotropin (hCG),(IUI), or intercourse if more than two follicles >15 mm diameter are seen.

- frequencies of congenital malformations and spontaneous abortion are not increased in pregnancies after clomiphene therapy.

- An absent or inadequate midcycle (LH) surge may result in a failure to ovulate or a short luteal phase, despite clomiphene-induced follicular development.

- exogenous hCG (single-dose 10,000 international units [IM]) may be added to the regimen. It is given when transvaginal ultrasonography shows that the leading follicle has reached 18 to 20 mm in diameter

- Hot flashes are common, occurring in 10 to 20 percent of women

- abdominal distention and pain (5.5 percent), nausea and vomiting (2.2 percent), and breast discomfort (2 percent)

- Mood swings, depression, and headaches

- Side effects of clomiphene are not dose related, as they can occur at the 50 mg dose.

- Visual symptoms, such as blurring, double vision, and/or scotomata, develop in 1 to 2 percent of women and are usually reversible

- The use of clomiphene citrate for ovulation induction does not appear to be associated with an excess risk of ovarian or breast cancer

Gonadotrophins

- Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors.

Where gonadotrophins are prescribed, considerations include:

- cost and availability
- expertise required for use in ovulation induction
- degree of intensive ultrasound monitoring required
- lack of difference in clinical efficacy of available gonadotrophin preparations
- low dose gonadotrophin protocols optimise monofollicular development
- risk and implications of potential multiple pregnancy

Anti-obesity agents

- Pharmacological anti-obesity agents

- should be considered an experimental therapy in women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.

Laparoscopic ovarian surgery

- Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are **clomiphene citrate resistant**, with **anovulatory infertility** and **no other infertility factors**

- Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.

In-vitro fertilization

- In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF as third line therapy where first or second line ovulation induction therapies have failed.

- In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimised

- Antagonist cycle
- FSH preparation
- LH preparation
- Final trigger
- OHSS