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INFERTILITY MANAGEMENT

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INFERTILITY MANAGEMENT SERIES

HANDBOOK OF OVARIAN STIMULATION

Foreword
Nozer Sheriar

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Chapter 3

Stimulation Protocols for Intrauterine Insemination

Kalyani Shrimali, Ritu Hinduja

INTRODUCTION

Intrauterine insemination is one of the first lines of infertility treatments and assisted reproductive technologies (ART). It is the safest, least invasive, and cost-effective forms of assisted reproduction.

Ovarian stimulation aims at development of one or more of the ovarian follicles to reach the stage of maturity culminating in release of one or more mature oocytes ready for fertilization. Ovarian stimulation has been shown to significantly improve the outcome in IUI cycles. With the help of ovulation-inducing drugs, there is an increase in number of eggs for fertilization and also it helps patients with anovulatory cycles to overcome the subtle defect in the ovulatory function. When IUI is performed in unexplained subfertile couples, OI doubles the pregnancy rates, compared with IUI without OI.[1]

There are two mechanisms of ovarian stimulation: the first involves applying pharmacological agents that mimic endogenous gonadotropins (injectable gonadotropins) that directly stimulate ovarian follicular development through gonadotropin receptors; and the second involves pharmacological agents that manipulate and moderate endogenous gonadotropin production. These are the oral ovulation through moderating estrogen action, a major regulator of endogenous gonadotropin production.[2]

ORAL AGENTS FOR OVARIAN STIMULATION

Oral agents modulate estrogen action, hence endogenous gonadotropin production through direct effect on estrogen receptors, i.e. selective estrogen receptor modulators (SERMs), or through modulation of estrogen production (inhibition), i.e. aromatase inhibitors, or inhibition of the estrogen synthesis enzyme (the aromatase enzyme).

Clomiphene Citrate

Clomiphene citrate has been used as a first line ovulation inducing agent for over 40 years. CC is a nonsteroidal triphenylethylene derivative that exhibits both estrogen agonist and antagonist properties, i.e. SERM. CC mainly acts as antiestrogen.[3]

It is a SERM that stimulates endogeneous follicle-stimulating hormone (FSH) production and secretion by interrupting estrogen feedback to the hypothalamus and pituitary. Increased FSH release drives folliculogenesis at the level of ovary.[3]

Regimens of Clomiphene Citrate for Ovarian Stimulation

The regimen usually starts from the early follicular phase, that is second to the fifth day of the cycle for 5 days. There is no difference in pregnancy rate whether clomiphene is commenced on day 2, 3, 4, or 5 of the cycle, although there is perhaps a tendency to multiple follicular development the closer the agent is commenced to menses.

The dose required for achieving ovulation is dependent on the body weight. Although the effective dose of CC ranges from 50 mg/day to 250 mg/day. Most women respond to treatment with 50 mg (52%) or 100 mg (22%). Although higher doses are sometimes required, the success rates are usually very low (150 mg, 12%; 200 mg, 7%; 250 mg, 5%). Most women who fail to respond to 150 mg of CC will ultimately require alternative or combination treatments.[4,5] The usual recommended dose is 100 mg/day.

Pregnancy rates are highest in the early cycles of CC treatment (usually first three cycles) with a significant decline in the chance of achieving pregnancy beyond the third treatment cycle down to a very low chance beyond the sixth treatment cycle.[4]

Outcome[4]

- Pregnancy: 30%
- Failure (no pregnancy despite ovulation): 40%
- Resistance (no ovulation): 25%
- Antiestrogenic effect: 5%.

Generally speaking, failure to conceive after six ovulatory cycles of CC treatment should be regarded as a clear indication to expand the diagnostic evaluation to exclude other infertility factors or to change the treatment strategy when evaluation is already complete.[6]

Adverse Effects

Clomiphene citrate is in general a safe medication and usually well tolerated, with most of the side effects being relatively mild—multiple gestations, mild ovarian hyperstimulation being the most common. Other serious long-term adverse effects have been suggested, including increased risk of ovarian cancer.

- *Multiple gestation pregnancy*: The incidence reported for multiple pregnancy is approximately 8% with CC treatment. However, majority of multiple gestations are twins. Triplet and higher order pregnancies are rare.[7]

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- Side effects such as vasomotor hot flashes are also noted. Unusual visual symptoms (visual blurring or persistent after-images) are also noted in 1% to 2% of patients taking CC, which are likely due to antiestrogenic effects of CC on the visual cortex.
- *Severe ovarian hyperstimulation syndrome*: The incidence of severe ovarian hyperstimulation syndrome (OHSS) is difficult to predict in CC-treated group; though mild OHSS is relatively common, but does not require active management most of the time.[6]
- *Ovarian cancer*: There is an uncertain association of ovarian cancer that has been suggested in the past. The recent subsequent studies have been reassuring but the question of whether the treatment with ovulation-inducing drugs increases risk of ovarian tumors or cancer still remains unsettled and cannot be summarily dismissed.[8-10] It is best to limit a patient's lifetime exposure to CC to 12 treatment cycles, as additional cycles may place the patient at increased risk of borderline ovarian tumors.[11]

Failure of Clomiphene Citrate Treatment

In anovulatory infertility, the failure is divided into two groups:

1. *Clomiphene resistance*: Patient who fails to ovulate with CC ovarian stimulation, i.e. failure to achieve ovulation. This could be due to one of the two main reasons; insulin resistance [(women with polycystic ovarian syndrome (PCOS)] and inappropriate indication for CC treatment, e.g. use in women with ovulatory dysfunction due to medical disorders or in women with WHO type I or III anovulation.
2. *Clomiphene pregnancy failure*: Patients who ovulate in response to CC treatment but do not achieve pregnancy. These may be related to a variety of other underlying infertility causes such as male factor, endometriosis or tubal factor or endometrial receptivity factors.

Clomiphene citrate exerts undesirable antiestrogenic effects in the periphery (endocervix, endometrium, ovary, ovum, and embryo) that can not be avoided due to long half-life of CC isomers. This could explain the discrepancy between ovulation and conception rates observed in CC-treated patients, i.e. explain the clomiphene treatment failure (ovulation but no pregnancy).

Aromatase Inhibitors

Aromatase inhibitors have been used for the last decade as adjunctive treatments in breast cancer. They block the conversion of testosterone and androstenedione to estradiol and estrone, respectively, and hence inhibit the estrogen-negative feedback on the hypothalamic-pituitary axis. This leads to increased gonadotropin secretion, which in turn leads to ovarian follicular growth and development.[12]

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Letrozole is the commonly used aromatase inhibitors drug for ovulation induction. This is an off-label drug. According to the existing laws, the use of letrozole for OI alone is not allowed. Thus, it should be used only, if the local FDA approves it.

Ovulation and pregnancy rates with aromatase inhibitors such as letrozole and anastrozole appear to be promising, and these agents appear to have less antiestrogen effect on the endometrium, but the evidence on endometrial effects is conflicting, and most studies show equivalence with CC.[12-15]

The addition of letrozole to gonadotropin stimulation protocols decreases the gonadotropin requirement and increases the number of preovulatory follicles.[16,17]

Dosage

Letrozole is administered in doses of 2.5–5 mg/day for 5 days, starting from day 3 of the cycle.

Extended Letrozole Therapy

In a recent study conducted by Badawy et al., extended letrozole therapy (2.5 mg daily from day 1 of menses for 10 days) was used in CC-resistant PCOS women. They observed that the long letrozole protocol (10 days) can produce more mature follicles and subsequently, more pregnancies than the short letrozole therapy (5 days).[18]

Letrozole Step-up Protocol

Recently, a new protocol known as the letrozole step-up protocol has been reported by Mitwally et al. In this protocol, letrozole was administered in the step-up doses consisting of one, two, three, and four tablets of letrozole (2.5 mg) daily on menstrual cycle days 2, 3, 4, and 5, respectively. When compared with the standard CC protocol (CC 100 mg for 5 days, starting on day 3), the step-up letrozole protocol was associated with multifollicular development and a higher clinical pregnancy rates per treatment cycle (27.3% vs 11.8%, respectively).[19]

Adverse Effects

In 2005, Health Canada and the manufacturing company of letrozole issued a "Physician Warning Letter" on the off-label use of letrozole for fertility and the possibility of embryotoxicity, fetotoxicity, and teratogenicity found in rats.[20]

More recently, however, Tulandi et al.[21] retrospectively evaluated 911 newborns from letrozole and CC pregnancies. They found a 2.4% incidence of congenital malformations and chromosomal abnormalities in the letrozole group versus 4.8% in the CC group.[21]

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Tamoxifen Citrate

It is used as an alternative to CC or with CC or in CC-resistant patients. It is structurally related to SERM which has weak estrogenic effect on cervical mucus and the endometrium. This drug also is used as an "off-label" drug.

Dosage: 20–40 mg/day to be started from day 2 to day 5.

Adverse Effects

Similar to CC but also noted slight increase in endometrial hyperplasia and endometrial carcinoma.[22]

Contraindication

Liver toxicity, pituitary failure, gonadal failure pregnancies, ovarian cyst, and abnormal uterine bleeding.

Gonadotropins

Use of gonadotropins has revolutionized the management of infertility.

Use of intramuscular gonadotropins began in the 1960s. Gonadotropins may be urinary derived (human menopausal gonadotropin or hMG) or manufactured using recombinant DNA technology (recombinant FSH or rFSH). Over the last decade, recombinant human FSH has been the main preparation, and it can be self-administered subcutaneously.[23] The rFSH is more expensive per unit dose but has been reported to have greater purity and, therefore greater efficacy of action.

Human menopausal gonadotropin also contains a degree of LH activity and some researcher claim that additional LH effect leads to better follicular/oocyte development and as a result, higher pregnancy rates compared to rFSH. However, there is no published evidence for this, particularly in IUI cycles where there is "background" pituitary production of FSH and LH. This is in contrast to ovarian stimulation for IVF where there is often concomitant pituitary down regulation using gonadotropin-releasing hormone (GnRH) analogs.

Gonadotropins are used to treat infertility caused by anovulation, usually after other less complicated and costly methods have failed. Two groups of anovulatory disorders may require gonadotropin therapy: (1) hypogonadotropic amenorrhea (HA, also known as hypogonadotropic hypogonadism, hypothalamic amenorrhea, or WHO type I amenorrhea); and (2) PCOS also known as hyperandrogenic amenorrhea or WHO type II amenorrhea.[24,25]

A recent Cochrane review (2007) on the available results of gonadotropins suggested that gonadotropins might be the most effective drugs when IUI is combined with ovarian hyperstimulation.[26]

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Choice of Gonadotropins

The choice of gonadotropin to be used depends upon the day 2 plasma luteinizing hormone (LH)/FSH/estradiol (E2) levels. If serum LH is elevated, FSH containing gonadotropins are indicated, whereas if serum FSH is elevated (>10 mIU/mL), a combination of LH and FSH is used for ovarian stimulation. For ovarian stimulation in patients with hypogonadotrophic hypogonadism, a combination of LH and FSH is used.

Gonadotropin Regimens

Conventional regimen: In this protocol, a daily dose of 75–150 IU of gonadotropins is started from day 2 or day 3. Serial ultrasonography (USG) for follicular monitoring and serum E2 estimation is performed from day 8 onwards. This protocol has yielded acceptable pregnancy rates of up to 30%.

Low dose step-up: The use of a low dose step-up regimen of OI similar to that described by Franks and others (Messinis, 2005).[27] Following induction of menses with either progestogens or the oral contraceptive pill, FSH or hMG is commenced 2–3 days later at a dose no higher than 50–75 IU per day. The dose is not altered until there is no rise in the estradiol level or no increase in the follicle size on ultrasound assessment. If there is any evidence of an estrogen rise above baseline (even if no follicular development is seen), the existing dose is maintained and further assessment with ultrasounds and hormones are undertaken every 2–3 days. A rising estrogen level indicates follicular development. When there are 1–2 follicles, 17 mm in diameter or larger, and the estrogen level is about 1,200 pmol/L or 350 pg/mL; hCG 5,000–10,000 IU is administered (Fig. 3.1).

If no rise of estrogen above baseline is seen after 7 days of FSH/hMG, the dose can be cautiously increased by 25–50 IU per day above the previous

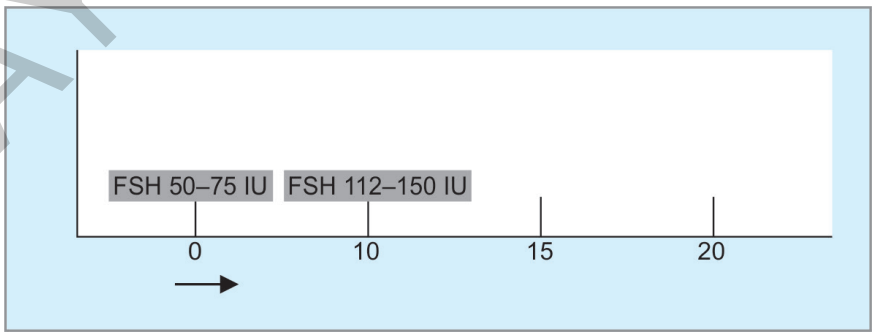

Fig. 3.1: Low dose step-up regimen.

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dose. The process of further assessment 5–7 days later can be repeated, with further increases in FSH/hMG only being necessary in the absence of an estrogen/follicular response.

Step-down regimen: In a step-down protocol, hMG/FSH therapy at a daily dose of 150 IU is started on day 2 and continued till a dominant follicle of greater than 10 mm is observed on transvaginal sonography (TVS). After this, the dose is decreased to 112.5 units intramuscular (IM) per day for 3 days, followed by 75 units IM per day for the next 3 days. This dose is then continued till the day of human chorionic gonadotropin (hCG) injection. The rest of the regimen is the same as in the step-up regime.

In almost 15% to 20% of the cycles, which have been stimulated with gonadotropins or CC, the exaggerated estradiol level due to the multifollicular development often provokes higher LH levels during the follicular phase or an untimely LH hormone surge, which leads to cycle cancellation. Therefore, in order to avoid interference from endogenous gonadotropin secretion, a combination of gonadotropins and GnRH analogs have been used for ovulation induction. Although GnRH analogs are routinely used in IVF cycles, their routine use in IUI cycles is not recommended. A recent Cochrane review has concluded that GnRH analogs do not significantly improve pregnancy rates in IUI.

Gonadotropin-IUI is a successful treatment but the greatest risk lies with multiple pregnancy, as a result of multiple follicular development.

The aim of treatment is to develop one leading follicle but many times there are other smaller follicles. Additionally, most physicians would accept two codominant follicles as an appropriate result for triggering of ovulation. As a result, twin pregnancies are relatively common and represent about one-fifth of all ongoing pregnancies.

Unlike clomiphene, where pituitary FSH is initially stimulated and then gradually falls in serum level toward midcycle, gonadotropin injections maintain a constant level of serum FSH throughout the follicular phase. As a result the normal process of dominant follicle selection is overridden and even middle-sized follicles can contain an oocyte with the capacity to cause pregnancy. This leads to a higher risk of not only twins but also higher order multiple pregnancies.

OVULATION TRIGGER

The ovulation is triggered by the administration of hCG injection when the following conditions are met: (1) Leading follicle is 18–20 mm; (2) The number of follicles more than 16 mm is not more than 4 or follicles more than 12 mm are not more than 8 in number; (3) Serum E2 is not more than 1,500–2,000 pg/mL (serum E2 level is estimated only, if the total number of follicles exceed 12 and if there is a potential chance of OHSS).

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CONCLUSION

Clomiphene citrate is an effective treatment for oligoovulation and anovulation. It helps to cause regular ovulation and increases pregnancy rates. It should be used only in properly selected patients and for the recommended amount of time. However, success rates with CC are low due to the antiestrogenic effects on the cervix (drying up the mucus) and endometrium.

Letrozole has been shown to be superior to clomiphene for patients with PCOS.

In women with infertility due to oligo or anovulation where treatment with CC or metformin is unsuccessful, fair evidence shows that gonadotropin treatment is effective.

Fair evidence shows that the pregnancy rate is higher with hypothalamic amenorrhea than it is with PCOS.

Protocols should attempt to minimize risk of multiple pregnancy and ovarian hyperstimulation syndrome.

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