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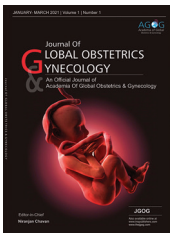
Review Article



Recent Trends in Ovulation Induction

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ABSTRACT

Ovulation induction involves mimicking the physiology of the normal menstrual cycle. Initiating medications for ovulation induction is a relatively simple treatment for female infertility. In recent years, new developments have occurred in ovulation induction therapy, which includes new information relevant to established methods of inducing ovulation and novel ways of administering these agents. This review discusses the recent trends in ovulation induction along with the guideline recommendations regarding the use of different medications for promoting ovulation.

Key words: Clomiphene citrate, Gonadotropins, Infertility, Letrozole, Ovulation induction

BACKGROUND

To understand the recent trends in ovulation induction, it is important to highlight the difference between ovulation induction and ovarian stimulation. Ovulatory disorders account for approximately 25% of female infertility cases.[1,2] Ovulation induction involves mimicking the physiology of the normal menstrual cycle. A normal menstrual cycle can be associated with one oocyte, one embryo, and one healthy full-term baby. On the other hand, ovarian stimulation involves applying supraphysiological doses of either hormones or oral ovulation induction agents to produce a multi-follicular response.

Ovulation induction should always be considered and practiced until *in-vitro* fertilization (IVF) procedure is initiated. Oral ovulation induction agents are to be used for cycles with planned relations. Gonadotropins are preferred for cycles involving intrauterine insemination (IUI). These cycles should normally be referred to as "ovulation induction" cycles, not "ovarian stimulation" cycles. Ovarian stimulation can be performed when a supraphysiological response is expected with the addition of oral agents or gonadotropins. This review discusses the recent trends in ovulation induction along with the guideline recommendations regarding the use of different medications for promoting ovulation.

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ORAL OVULATION INDUCTION AGENTS

Clomiphene Citrate (CC)

Mechanism of action

CC is one of the most common drugs used for ovulation induction. CC is a competitive estrogen antagonist, suppressing the estrogen receptors through the hypothalamic-pituitary-ovarian axis and the endometrium. Approximately, 85% of the administered dose of CC is eliminated after 6 days, although the traces may remain in circulation for much longer. Clinically, there is no evidence of any important consequence of the isomer of CC that is usually found as detectable traces in circulation. CC depletes the estrogen receptors resulting in false interpretation by the hypothalamus, thereby increasing the gonadotropin-releasing hormone (GnRH) pulse frequency in ovulatory women or by increasing the pulse amplitude in anovulatory women. This leads to an increase in the production of follicle-stimulating hormone (FSH) resulting in an increased response from the ovary. The luteinizing hormone (LH) surge normally occurs 5–12 days after the last dose of CC is taken.

ADMINISTRATION AND DOSING

It is suggested to start with the least dose of CC and observe for the clinical response. However, sometimes it takes 1–2 cycles to monitor and arrive at the correct dosage. Hence, in general, the treatment can be initiated from a starting dose of 100 mg. If the patient hyper responds at this dose, it is advised to cancel the current cycle and start with a lower dose in the next cycle. The chances of hyperstimulation due to CC are extremely rare and when more than three eggs are produced in one cycle, there are chances of multiple pregnancies.

Ideally, CC is started at a dose of 100 mg per day on cycle day 2 until cycle day 6. The older practice of initiating CC on cycle day 5 or 6 should be stopped as the desired outcomes cannot be achieved. The follicular phase is divided into two parts – the early phase involves the recruitment of eggs and the later stage involves the growth of eggs. When the treatment is started after cycle day 5 or 6, only the naturally recruited eggs in the current state will grow. This largely limits the efficacy of CC.

LUTEAL PHASE SUPPORT

Human chorionic gonadotropin (hCG) is normally used as a trigger for provoking ovulation in the luteal phase. The hCG molecule has two components, the alpha and beta sub-units. The alpha sub-unit of hCG is biochemically similar to LH, causing the oocyte to falsely interpret an LH surge. This results in a shift from an early estrogenic metabolism of granulosa cells and estrogen to the luteal metabolism of theca cells and progesterone.

The shift of metabolism in the oocyte, from granulosa in estrogen to theca of progesterone is often incomplete. Therefore, hCG trigger is usually given as a fixed dose of LH, as per the levels of E2 in the follicular phase; resulting in an idiopathic luteal phase effect. Hence, luteal phase support is given for all cycles with hCG or GnRH agonists as a trigger.

NUMBER OF CYCLES

The American Society for Reproductive Medicine recommends a maximum of 9 cycles with CC in a woman's lifetime. However, not more than 3–4 cycles are attempted in clinical practice. If pregnancy is not achieved with CC within 3–4 cycles, it is advised to shift to other ovulation induction agents.

CLOMIPHENE RESISTANCE

When a maximum dosage of CC is given for the maximum duration and ovulation has not been achieved, it is called as clomiphene resistance. On the other hand, clomiphene failure is when ovulation has been achieved but it does not result in any pregnancy. Evaluation of clomiphene resistance or clomiphene failure serves as an important step to determine the further treatment plan.

Limitations

Although an ovulation rate of 80% is achieved with CC, the cumulative pregnancy rate at the end of 4 cycles remains at only 35–40%. Earlier, gonadotropins were the only option available after CC treatment. However, recently, the aromatase inhibitor letrozole is widely considered in patients with inadequate response to CC.

LETROZOLE

Mechanism of Action

Letrozole is an aromatase inhibitor with a unique mechanism of action and short half-life. It inhibits the conversion of androgens to estrogen within the ovary. Letrozole does not have any effect on the estrogen receptors and its action within the ovary results in a mono-follicular response. This mechanism of action is in contrast to CC as estrogen production is advanced by induced FSH, however, the hypothalamus responds to this estrogen with a negative feedback mechanism. Letrozole provides an ovulation rate per cycle of 70%-84% with a pregnancy rate of 20%-27%. Although hot flushes may occur, these are infrequent due to the short half-life of letrozole.[3]

Due to its short half-life, letrozole is not available in the bloodstream when the embryo is formed. Thus, letrozole use does not increase the risk of congenital abnormalities in newborns as cited in various literature reports.

Guidelines on Ovulation Induction

The current guidelines clearly stratify when to use CC and letrozole as the first line of therapy for ovulation induction. In general, it is suggested that letrozole should be preferred as the first choice in women who may be more responsive to this therapy, such as women with polycystic ovaries (PCO) or with body mass index >30. It results in an increased live birth rate than CC in these women.

CC should be preferred as the first choice only when low to normal response is expected. When three cycles of letrozole treatment does not result in any pregnancy, CC can be used.

Current Dose Recommendations

Indian guidelines recommend the following for using letrozole for ovulation induction:

Letrozole should be started at a dose of 2.5 mg once daily for 5 days, starting from cycle day 3 to day 7. If ovulation does not occur at this dose, it can be increased to 5 mg or up to 7.5 mg/day. A maximum of three consecutive cycles are to be attempted or until the occurrence of pregnancy, though various international studies recommend letrozole for a much longer duration.

IUI with Oral Ovulation Induction Agents

Oral ovulation induction agents should be used for IUI only in certain cases such as erectile dysfunction, hypospadias, or due to surgeries in women such as cervical biopsy or conization of the cervix. IUI with oral ovulation induction agents does not improve the pregnancy rates. Various studies recommend the use of gonadotropins for effective IUI outcomes as the success rates are very high and it is also cost-effective.

Non-IVF Gonadotropin Cycles

The important differentiation between IUI and oral ovulation induction is that, in IUI, ovulation with gonadotropins will occur much sooner at around cycle day 10 unlike at cycle day 14 for other ovulation induction agents. For determining the starting dose for IUI, the factors considered are age, Anti-Mullerian Hormone,and antral follicle count that further define the patient having PCO or otherwise.

Dosage

For Non PCO women irrespective of age, above or below 35 years, the starting dose of gonadotropins should be 150 IU. For women with PCO <35 years, it should be started with 75 IU and for >35 years at 150 IU to obviate the effect of age on ovarian reserve and fertility.

Monitoring

Gonadotropins are usually started on day 2 of the cycle for up to 5 days. At the end of 5 days, an ultrasound monitoring is done. If 2–3 follicles >10 mm are observed, the same dose is continued. For 4–6 follicles, dose can be continued or tapered. In case of more than six follicles, it is advised to cancel the treatment cycle due to the risk of multiple pregnancies. If all the follicles are <10 mm, consider increasing the dosage. For women with PCO, dosage can be increased by half of the starting dose and in case of poor responders, dosage is to be doubled. Continue gonadotropins until the first follicle reaches 18 mm in size and trigger for ovulation.

Letrozole and Gonadotropins

Letrozole is a preferred combination with gonadotropins if required, rather than CC.

GNRH ANTAGONISTS FOR IUI CYCLES

The benefit with the addition of GnRH antagonists for IUI is still not clear, however, it does not cause any harm. A recent study by Monraisin *et al*. supports the use of GnRH antagonists for IUI as it greatly improves the pregnancy rates and the live birth rate recorded is 11.4%.

TRIGGER

hCG is normally used as a trigger. Recombinant hCG is administered at a dose of 10,000 units or as one pre-filled syringe. Ovulation is documented on the basis of ultrasound monitoring. The chances of luteinized unruptured follicle syndrome are rare if hCG has been administered properly. Hence, there is no need to repeat the dosage. Trigger administration is usually withheld if there are more than four follicles.

MONITORING OF CYCLES

Monitoring of ovulation induction is done minimally, twice in a cycle. Satisfactory pregnancy and birth rates have been recorded with minimal monitoring protocol.

SUPPLEMENTS TO CC

Metformin

Metformin was widely used earlier in combination with CC for induction of ovulation, however, there is no advantage to it unless in women with metabolic syndrome. Literature states that the addition of metformin did not increase the pregnancy rates or decrease the miscarriage rates.

CONCLUSION

Ovulation induction provides a solution for the vast majority of women with infertility. Over the past 20 years, significant progress has been achieved in ovulation induction. CC is one of the most common drugs used for ovulation induction. Recently, the aromatase inhibitor letrozole is widely considered in patients with inadequate response to CC. Unlike CC, they do not carry an antiestrogenic effect on the endometrium.[4] Given the advantages of aromatase inhibitors, they can be used to replace CC as ovulation-inducing drugs.[4] Other methods such as the use of gonadotropins have also been recommended. Gonadotropins are more effective than CC but are expensive and associated with higher risk for ovarian hyperstimulation syndrome and multiple gestations.[4] However, the treatment of ovulation induction should be individualized.

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