ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection

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Objective: To investigate flexibility in starting controlled ovarian stimulation at any phase of the menstrual cycle in infertile women undergoing treatment with assisted reproduction.
Design: Retrospective cohort study.
Setting: Academic tertiary-care medical center.
Patient(s): At total of 150 infertile patients undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment. Ninety of the women also underwent frozen embryo transfer (FET) procedures.
Intervention(s): Depending on the phase of the menstrual cycle when ovarian stimulation was started, three groups of patients were identified, namely: conventional group (ovarian stimulation started in the early follicular phase), late follicular phase group, and luteal phase group. When dominant follicles were observed, final oocyte maturation was triggered with the use of GnRH agonist and hCG. In all three groups, viable embryos were cryopreserved for subsequent transfer.
Main Outcome Measure(s): Primary outcome: number of mature oocytes retrieved. Secondary outcomes: fertilization rate, viable embryo rate per oocyte retrieved, cancellation rate, and clinical pregnancy outcomes from FET cycles.
Results(s): There were no differences in the mean number of mature oocytes retrieved in the conventional group, late follicular phase group, and luteal phase group (5.7 $\pm$ 3.6, 5.2 $\pm$ 3.7, and 5.2 $\pm$ 3.9, respectively). Similarly, no significant differences were observed in the viable embryo rate per oocyte retrieved (37.9%, 38.5%, and 43.6%), clinical pregnancy rates (41.5%, 45.5%, and 38.9%), and implantation rates (30.7%, 30.2%, and 27.1%) in the three groups.

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Conclusion(s): All three ovarian stimulation protocols were observed to be equally effective. These results demonstrate that ovarian stimulation can be commenced on any day of the menstrual cycle.

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Key Words: controlled ovarian stimulation, flexible start for ovarian stimulation, frozen embryo transfer

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The conventional approach to ovarian stimulation for assisted reproduction treatment is to commence fertility drug administration in the early follicular phase. This approach is often challenging for patients given the diversity in their personal schedules. Also, it is particularly problematic for women recently diagnosed with cancer requiring radiation and/or chemotherapy that may compromise their future fertility potential. Consequently, a more flexible approach to providing ovarian stimulation is desirable.

Recently, several investigators have reported that in women with newly diagnosed cancer requiring urgent oncologic treatment, emergency fertility preservation is possible by ignoring the prevailing custom and commencing ovarian stimulation at any time in the menstrual cycle (1–4). In such situations, starting ovarian stimulation at no fixed time during the menstrual cycle, GnRH antagonist (GnRH-ant) is used for suppressing pituitary release of gonadotropins, thereby preventing a premature LH surge (1–4).

Although the numbers of oocyte retrieved and numbers of viable embryos available per cycle do not appear to be compromised by varying the onset of timing of ovarian stimulation, there are two challenges and limitations. First, the duration of gonadotropin use appeared to be longer when ovarian stimulation was commenced randomly than when it was commenced per convention. Second, using letrozole to prevent the level of estrogen rising to unacceptably high levels in women with estrogen-sensitive cancer resulted in a lower proportion of mature oocytes (1). To date, the random-start protocol has been used only in women with recently diagnosed cancer, and most of them have not undergone frozen embryo transfer. Furthermore, reviews in the literature on stimulation protocols used in assisted reproduction in general have reported a difference in the synchronization of follicular recruitment and growth when the GnRH-ant protocol is compared with the GnRH-a protocol (5, 6).

In our tertiary-care center in China, patients come from many different districts; about 78% of our patients are not from our surrounding locale. For many of these out-of-district patients, the challenges of traffic congestion and work pressure result in several days being required for them in travel to reach our hospital clinic. Consequently, when they arrive for assisted reproduction treatment, they often are in different phases of the menstrual cycle. These women express a strong desire to save time and wish to commence infertility therapy as soon as possible. So it became evident to us that there was a pressing need to have an ovarian stimulation protocol that is more flexible.

In 2009, we found that ovarian stimulation with gonadotropins could be started in the luteal phase with the use of letrozole and clomiphene citrate (CC); our experience and results were published 2 years ago (7, 8). We used the freeze-all embryo policy. We observed no LH surge in those cycles, and the likelihood of ovarian hyperstimulation syndrome (OHSS) was low. Our protocol included freezing all of the embryos for transfer in a subsequent cycle. No differences in birth defects were observed between luteal-phase ovarian stimulation and conventional ovarian stimulation (9). In fact, the risk of congenital anomalies was found to be correlated with infertility duration and the occurrence of multiple pregnancies, not with the ovarian stimulation protocol. We hypothesized that endogenously produced progesterone in the luteal phase could prevent a premature LH surge with ovarian stimulation. Furthermore, the administration of exogenous progestational agents, such as medroxyprogesterone acetate (MPA), was found to prevent a premature LH surge in women undergoing controlled ovarian hyperstimulation (COH) (10). An additional advantage of using MPA is that it is administered orally, making its use more convenient for patients.

Because both endogenously produced progesterone and exogenously administered progestational agents did not prevent the response to ovarian stimulation, it became feasible to consider using a more flexible approach to ovarian stimulation. In early follicular phase, MPA can be used to prevent the premature LH surge, whereas in the luteal phase, the endogenous production of progesterone is sufficient to prevent the occurrence of a premature LH surge when ovarian stimulation is used. Based on this thesis, the commencement of ovarian stimulation late in the follicular phase can be followed by using GnRH agonist (GnRH-a) to induce a luteal phase. However, if the flare-up phenomenon of gonadotropin release with the use of GnRH-a is not sufficiently effective, exogenous MPA can be added to complement the endogenous production of progesterone.

The objective of the present study was to compare the cycle and pregnancy outcomes of a more flexible approach to starting ovarian stimulation with the conventional regimen of ovarian stimulation in infertile patients undergoing treatment with assisted reproduction.