Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles

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Objective: To explore the feasibility of luteal-phase ovarian stimulation using hMG and letrozole in terms of ovarian response and pregnancy outcome using frozen-thawed embryo transfer.
Design: A prospective cohort study.
Setting: Academic tertiary-care medical center.
Patient(s): Two hundred forty-two female patients undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment.
Intervention(s): Ovarian stimulation was initiated with hMG 225 IU and letrozole 2.5 mg daily after spontaneous ovulation. Letrozole administration was stopped when the dominant follicles reached diameters of 12 mm. Ovulation was induced with a GnRH agonist 100 μg when at least three follicles reached diameters of 18 mm or one dominant follicle reached 20 mm. The highest quality embryos were extracted and cryopreserved for later transfer.
Main Outcome Measure(s): The primary outcome measured was the number of oocytes retrieved. Secondary outcomes were the clinical pregnancy rate, ongoing pregnancy rate, and implantation rate after frozen embryo transfer (FET) cycles.
Result(s): Of the 242 women enrolled in the study, all participants succeeded in producing oocytes and 227 women had highest-quality embryos to cryopreserve. The average number of oocytes retrieved was 13.1, producing an average of 4.8 highest quality embryos. Moreover, no cases experienced a premature LH surge or moderate/severe ovarian hyperstimulation syndrome during the stimulation cycles. In FETs, the clinical pregnancy rate, ongoing pregnancy rate, and implantation rate were 55.46% (127/229), 48.91% (112/229), and 40.37% (174/431), respectively. Of all the pregnancies in the study, 68 resulted in live births and 44 were ongoing.
Conclusion(s): Luteal-phase ovarian stimulation is feasible for producing competent oocytes/embryos in women undergoing IVF/ICSI treatments, with optimal pregnancy outcomes in FET cycles. (Fertil Steril® 2014;101:105–11. ©2014 by American Society for Reproductive Medicine.)
Key Words: Ovulation induction, luteal phase, human menopausal gonadotropin, letrozole, frozen embryo transfer, LH surge, OHSS

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Ovarian follicles undergo dynamic morphological and endocrinological changes during the human menstrual cycle. The traditional process of folliculogenesis involves the recruitment of various antral follicles in each ovary during the late luteal phase of the preceding menstrual cycle. Then, during the initial or middle stage of the follicular phase, a single follicle is selected, while the others undergo atresia (1, 2). However, some studies have demonstrated that small antral follicles observed during the luteal phase may not necessarily be in atresia but may rather be in the early stages of follicular development (3, 4). This indicates waves of follicular development within a single interovulatory period, with the presence of healthy follicles in the luteal phase as determined by oocyte and granulosa cell viability (3, 4). Luteal-phase in vitro maturation provides sound evidence that the oocytes retrieved during the luteal phase can be competent to mature and be fertilized (5, 6). These observations suggest the possibility that follicles are continuously available for stimulation by gonadotropins during the menstrual cycle. However, standard regimens of ovarian stimulation are started during the early follicular phase of the menstrual cycle. One of the disadvantages of follicular-phase ovarian stimulation is that with the development of multiple follicles stimulated by exogenous gonadotropin, a premature LH surge is sometimes elicited. This is due to the positive feedback of high E_2 on the pituitary and results in premature luteinization and suboptimal oocyte quality. Therefore, GnRH analog cotreatment is believed to be necessary to prevent the premature LH surge that occurs in the current practices, but this regimen makes the stimulation complex (7). Another detriment of ovarian stimulation is the serious complications caused by ovarian hyperstimulation syndrome (OHSS), a rare but potentially life-threatening condition.

Few studies consider the possibility of performing ovarian stimulation during the luteal phase of the menstrual cycle except for a small number of case reports on cancer patients (8–10). In the context of fertility preservation, luteal-phase administration of FSH and a GnRH antagonist was reported to produce mature oocytes/embryos for cryopreservation (8–10), but no data on pregnancy outcomes were available in the limited samples. This study is not generalized to all infertile women to evaluate the efficacy of ovarian stimulation in the luteal phase.

We drew inspiration from a case that initiated ovarian stimulation with hMG and letrozole during the luteal phase, with a satisfactory ovarian response and a pregnancy outcome. So we extended the concept to a routine IVF setting that can be used independently of menstruation. Given the asynchrony of the endometrium and embryo in such settings, all fertilized oocytes had to be cryopreserved for a later transfer.

This study aimed to explore the efficacy of initiation of ovarian stimulation in the luteal phase using hMG and letrozole in terms of ovarian response characteristics and pregnancy outcomes of frozen embryo transfers (FETs).

MATERIALS AND METHODS

Study Setting and Patients

A prospective cohort study was conducted at the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiaotong University School of Medicine. Women undergoing IVF/intracytoplasmic sperm injection (ICSI) regimens for the treatment of infertility were recruited between July 2011 and September 2012. The study protocol was approved by the Ethics Committee (Institutional Review Board) of the Ninth People's Hospital of Shanghai. The trial was conducted according to the Declaration of Helsinki for medical research. All participants provided informed consent after counseling for infertility treatments and routine IVF procedures.

Patients planning to undergo IVF/ICSI treatments were eligible to participate. The inclusion criteria were women aged 20–38 years with a body mass index (BMI) of 18–30 kg/m^2, spontaneous ovulation, infertility caused by tubal factor infertility or male factor infertility, or unexplained infertility. The definition of spontaneous ovulation included at least one of the following criteria: an elevated LH level in the urine as measured by a urine test, the presence of collapsed follicles in an ultrasound examination, or an increase in the serum P level to 2.0 ng/mL or higher. Study exclusion criteria were [1] clinically significant systemic disease such as renal failure, [2] documented ovarian failure or basal FSH value >15 IU/L, [3] endometriosis grade 3 or higher, [4] subjects who had previous unsuccessful IVF/ICSI treatments, [5] any contraindications to ovarian stimulation treatment, and [6], for subjects prepared to undergo luteal-phase stimulation, largest antral follicle diameter of no more than 8 mm in 1–3 days after ovulation, as evidenced by ultrasound exam. Given that this research was exploratory, we planned to include 200 women.

Procedures

All participants were asked to prevent getting pregnant by using mechanical contraception or refraining from intercourse during their periovulatory phase. Participants were required to test their urine using an LH kit beginning on cycle day 10. When the LH surge indicator line appeared, they came to the clinic for an ultrasound and a serum hormone test. These ultrasound scans, along with serum P concentration testing, helped detect spontaneous ovulation. For the patients with follicles of <8 mm on 1–3 days remaining after ovulation, an hMG (Anhui Fengyuan Pharmaceutical Co.) 225 IU IM injection and letrozole (Jiangsu Hengrui Medicine Co.) 2.5 mg were administered every day; weekly follow-up visits were conducted. For monitoring, a transvaginal ultrasound examination was performed to record the number of developing follicles, and serum FSH, LH, E_2, and P_4 concentrations were measured. Letrozole administration was stopped when the dominant follicles each reached diameters of 12 mm. Daily administration of medroxyprogesterone acetate (MPA) 10 mg was added to the treatment regimen for cases in which on day 12 postovulation follicle size was smaller than 14 mm and stimulation needed to continue for several more days. This was done to postpone menstruation and avoid oocyte retrieval during menstruation, to prevent the risk of infection from the procedure. The final stage of oocyte maturation was induced with triptorelin (Decapeptyl, Ferring GmbH) 100 μg, injected when at least three follicles reached diameters of 18