ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Effect of the initiation of progesterone supplementation in in vitro fertilization–embryo transfer outcomes: a prospective randomized controlled trial

Jun Gao, Ph.D., Fang Gu, M.D., Ben-Yu Miao, Ph.D., Ming-Hui Chen, Ph.D., Can-Quan Zhou, M.D., and Yan-Wen Xu, Ph.D.

Guangdong Provincial Key Laboratory of Reproductive Medicine, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China

Objective: To analyze the influence of the start point of luteal support on clinical pregnancy rate, implantation rate, and live birth rate of in vitro fertilization and embryo transfer (IVF-ET) cycles.
Design: Single-center prospective randomized controlled trial.
Setting: University-affiliated IVF unit.
Patient(s): Women ≤35 years of age with day 3 FSH levels <15 mIU/mL, who were undergoing their first IVF-ET cycles and received ovarian stimulation with the use of a GnRH agonist long protocol.
Intervention(s): The patients were randomized on the day of hCG trigger to receive luteal phase support either 1 day after oocyte retrieval (group A) or on the day of oocyte retrieval (group B).
Main Outcome Measure(s): Clinical pregnancy rate, implantation rate, miscarriage rate in the first trimester of pregnancy, and live birth rate per embryo transfer cycle.
Result(s): Two hundred thirty-three patients were enrolled in this study: 117 were assigned to group A and 116 to group B. The clinical pregnancy rate (group A vs. group B: 55.3% vs. 51.5%), implantation rate (38.4% vs. 38.0%), and miscarriage rate (7.7% vs. 7.5%) were similar between the two groups. The live birth rate also did not significantly differ between the two groups (45.7% vs. 46.6%).
Conclusion(s): Our study indicated that the initiation of progesterone supplementation 1 day after oocyte retrieval did not decrease the clinical pregnancy rate, implantation rate, or live birth rate in women undergoing IVF-ET cycles with the use of the GnRH agonist long protocol.
Clinical Trial Registration Number: ChiCTR-IPR-14005293. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Luteal phase support (LPS), initiation of progesterone supplementation, in vitro fertilization, implantation window, randomized study

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/20652-24595

Pituitary down-regulation with the use of GnRH analogues in assisted reproductive technology (ART) and disruption of granulosa cells (GCs) during oocyte retrieval results in a dysfunctional luteal phase for some patients. In addition, premature luteolysis occurs owing to inhibition of LH release by negative feedback from superphysiologic E_2 levels during controlled ovarian stimulation (1). Therefore, luteal phase support (LPS) is an integral part of in vitro fertilization and embryo transfer (IVF-ET) cycles treated with the use of GnRH analogues. However, there is significant debate on the timing, dose, and routes of progesterone (P) administration. It has been previously proposed that early P administration may be beneficial to ET owing

Received June 29, 2017; revised September 14, 2017; accepted September 26, 2017.
J.G. has nothing to disclose. F.G. has nothing to disclose. B.-Y.M. has nothing to disclose. M.-H.C. has nothing to disclose. C.-Q.Z. has nothing to disclose. Y.-W.X. has nothing to disclose.
Supported by the Special Fund for Scientific Research in the Public Interest (grant no 201402004), the National Natural Science Foundation of China (grant no 81370765), and the Science and Technology Program of Guangzhou, China (grant no 201300000097). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Reprint requests: Yan-Wen Xu, Ph.D., and Can-Quan Zhou, M.D., Reproductive Center, First Affiliated Hospital, Sun Yat-sen University, Zhongshan 2 Road, Guangzhou, Guangdong, People's Republic of China (E-mail: zhoucanquan@hotmail.com or xuyanwen663000@126.com).

Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2017.09.033

to the uterine smooth muscle–relaxing effect of P (2). Conversely, ART cycles may be associated with advancement of the endometrium, leading to embryo-to-endometrial asynchrony and implantation failure (3). Administration of P too early may further expand this asynchrony (4). In China, most centers start P administration on the day of oocyte retrieval. The purpose of the present study was to investigate the impact of the start point of LPS (1 day after oocyte retrieval vs. the day of oocyte retrieval) on the outcome of IVF-ET cycles.

MATERIALS AND METHODS

Patients

This randomized controlled trial was conducted from October 1, 2014, to January 31, 2015, at the Reproductive Center of the First Affiliated Hospital of Sun Yat-sen University in Guangzhou, China. Indications for IVF included tubal factors, male factors, a combination of the two, and unexplained factors. The inclusion criteria were as follows: 1) a regular menstrual cycle of 25–35 days; 2) $\leq$35 years of age; 3) basal serum FSH concentration $<$15 mIU/mL; 4) no previous IVF-ET cycle; and 5) had not undergone gonadotropin treatment $\leq$3 months before the study start. Patients with polycystic ovarian syndrome, endometriosis, uterine malformations, such as bicornuate uterus and uterine cavity adhesion, ovarian tumor, recurrent spontaneous abortion, elevated serum value of P on trigger day ($\geq$1.5 ng/mL), and chromosomal abnormalities were excluded from participation in the study.

Ethical Approval

This study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University (no 2014–59). All of the patients provided written informed consents to participate in the study, which was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Our study was registered in the Chinese Clinical Trial Registry with the registration number ChiCTR-IPR-14005293. The authors have no conflicts of interest to declare.

Sample Size

It was hard to define sample size based on references, because there were no statistically significant differences in earlier studies comparing day 0 and day 1 P initiation (5). One study found a 24% difference (47.5% vs. 71.4%, respectively) in the pregnancy rate when LPS was delayed up to 6 days versus 3 days after oocyte retrieval (6). Based on that report, we calculated that 103 subjects per group would be adequate to detect a significant difference between treatments with 90% power and a two-sided significance level of 0.05. To allow for dropouts ($\sim$10%), the recruitment target was 113 subjects per group (total 226 participants).

Down-Regulation Protocol

All patients underwent pituitary desensitization initiated by the administration of GnRH agonist (GnRH-a) at the midluteal phase (day 20–22) of the preceding IVF-ET cycle. There were two types of protocol. In the long-acting GnRH-a group, patients received 1.0 mg diphereline acetate (Diphereline 3.75 mg; Ipsen) via a single intramuscular (IM) injection. In the short-acting GnRH-a group, patients were subcutaneously administered 0.1 mg diphereline acetate (Diphereline 0.1 mg) daily before hCG administration.

Controlled Ovarian Hyperstimulation and IVF

Pituitary down-regulation was confirmed on days 3–5 of the cycle by sonographic detection of endometrial thickness $\leq$5 mm and suppressed ovaries (no antral follicles $\geq$10 mm in size), serum E_2 levels of $\leq$50 pg/mL, and LH levels of $\leq$5 IU/L. After confirmation of pituitary down-regulation, gonadotropin stimulation was induced daily with the use of human recombinant FSH (112.5–300 IU; Gonal-F; Serono). We adjusted the initial and ongoing dosage according to the patient's age, basic FSH level, body mass index, antral follicle count, and follicular growth response. Ovulation was induced with the use of 250 μg recombinant hCG (Ovidrel; Serono) when the diameters of at least three follicles were $>$17 mm or at least two follicles were $>$18 mm diameter. Ovum retrieval was performed 34–36 hours after ovulation induction with the use of vaginal ultrasound guidance.

Standard laboratory protocols for conventional IVF and intracytoplasmic sperm injection (ICSI) were followed (7). ICSI was performed only for male factor infertility according to the European Society of Human Reproduction and Embryology guidelines (8). Cleavage-stage embryos were transferred at 72 hours and blastocysts were transferred at 120 hours after oocyte retrieval. Embryo quality was evaluated according to the Istanbul Consensus Workshop on Embryo Assessment (9). As a rule, and when available, for day 3 ET, two embryos were transferred to women $<$35 years of age and three embryos were transferred in women who were 35 years of age or older. A maximum of two embryos could be transferred for day 5 ET. ET was cancelled if the patients presented with one of the following conditions: ovarian hyperstimulation syndrome, abnormal endometrium (endometrial thickness $\leq$6 mm on ultrasound, fluid in cavity, or endometrial polyps), P level $\geq$1.5 ng/mL on the hCG administration day, having a fever on the ET day, or absence of available embryos. Luteal phase was supported with IM injection of natural P in oil (60 mg daily). The β-hCG level was measured 12–14 days after embryo transfer. Biochemical pregnancy was confirmed when the β-hCG level was $>$25 IU/L. Clinical pregnancy was confirmed based on the detection of gestational sacs by means of ultrasonography 4–5 weeks after ET. Miscarriage in the first trimester of pregnancy was defined as the spontaneous loss of a clinical pregnancy before 12 completed weeks of gestational age.

Randomization, Blinding, and Grouping

Eligible subjects were randomized with the use of a computer-generated random number list in blocks of four to either group