ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Increased odds of live birth in fresh in vitro fertilization cycles with shorter ovarian stimulation

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Objective: To investigate the impact of prolonged ovarian stimulation on pregnancy outcomes in IVF cycles with fresh day 3 ET.
Design: Retrospective cohort study.
Setting: University-affiliated center.
Patient(s): All patients initiating their first IVF cycle with fresh day 3 ET. Prolonged ovarian stimulation was defined as a duration of more than two standard deviations (95th percentile) for the study cohort (i.e., >13 days).
Intervention(s): None.
Main Outcome Measure(s): Live birth rate was considered the primary outcome and was compared between patients undergoing ovarian stimulation for ≤13 days and >13 days. Odds ratios (OR) with 95% confidence intervals (CI) for all pregnancy outcomes after day 3 ET were calculated. The OR for live birth was adjusted using logistic regression.
Result(s): A total of 6,410 and 339 patients underwent ovarian stimulation for ≤13 days and >13 days, respectively. There were no differences in the demographics or mean number of day 3 embryos transferred between the two groups. Ovarian stimulation ≤13 days was associated with increased odds of clinical pregnancy (OR 2.15, 95% CI 1.19–3.89) and live birth (OR 2.35, 95% CI 1.25–4.43). The increased odds for live birth in the ≤13-day group remained unchanged after logistic regression. Patients with clinical pregnancies in the >13-day group were younger (34.6 ± 4.91 years) compared with those who did not conceive (38.2 ± 4.72 years).
Conclusion(s): Our findings suggest that ovarian stimulation ≤13 days is associated with increased odds of clinical pregnancy and live birth. In patients undergoing ovarian stimulation >13 days, younger age is associated with live birth. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, prolonged ovarian stimulation, prolonged gonadotropin stimulation, pregnancy outcomes

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In vitro fertilization has gained popularity during the past 2 decades as a treatment modality to overcome infertility. Global data suggest that approximately 4,461,309 IVF cycles were initiated between 2008 and 2010, resulting in the birth of 1,144,858 live-born infants (1). In the United States, 160,521 IVF cycles were performed across 467 fertility clinics, contributing to 1.6% of all live births in 2013 (2). The increasing use and success of IVF worldwide has been predominantly due to the optimization of associated clinical and laboratory protocols (3). However, several patient or laboratory-related variables, either modifiable or nonmodifiable, may still impact overall IVF outcomes.

Ovarian stimulation is one such modifiable variable that has been evaluated extensively since the inception of IVF. Specifically, previous studies have investigated the effect of various ovarian stimulation protocols (step-down or step-up; long or short), gonadotropin type and combinations, and gonadotropin doses on IVF outcomes (4–8). Of these, at least two studies (6, 7) have reported a detrimental effect of prolonged ovarian stimulation on IVF outcomes. Prolonged ovarian stimulation, and therefore a higher cumulative gonadotropin dose, is thought to directly impact oocyte/embryo quality or the early implantation environment (8). For example, in vitro studies in mice have shown that exposure to high doses of gonadotropins can accelerate nuclear maturation and induce chromosomal abnormalities (9). Furthermore, the

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aneuploidy rates of luteinized human granulosa cells (GCs) were noted to be higher with increasing doses of gonadotropins (10). Prolonged ovarian stimulation is also known to induce embryo–endometrial asynchrony (8, 11), thereby decreasing the implantation potential of embryos.

Although these findings are notable, several clinical studies reporting lower pregnancy rates (PRs) and live birth rates in IVF cycles with prolonged ovarian stimulation included patients with diminished ovarian reserve (4) and polycystic ovarian syndrome (PCOS), a known risk factor for longer stimulation (6, 7). Furthermore, these studies also included a wide range of ovarian stimulation protocols (5–7). Thus, in this study, we investigate the impact of prolonged ovarian stimulation on pregnancy outcomes in patients with non-PCOS and normal responders undergoing IVF cycles with fresh day 3 ET.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

All couples initiating their first IVF cycle with fresh day 3 ET at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine between January 2008 and June 2015 were analyzed for potential inclusion. For the purpose of this study, only patients undergoing ovarian stimulation with GnRH antagonist (GnRH-a)-based protocols were included. Patients with known PCOS as diagnosed by the Rotterdam criteria, patients with diminished or poor ovarian reserve defined by cycle day 2/3 FSH level >12 mIU/mL or cycle day 2/3 antimüllerian hormone level <1 ng/mL, and any prior IVF-ET cycles were excluded. Also excluded from the analysis were any IVF cycles canceled before oocyte retrieval, with incomplete records, or those using surgically retrieved sperm or donor oocytes. Our analysis was also limited to patients undergoing fresh ET of cleavage-stage (day 3) embryos. The Weill Cornell Medical College institutional review board approved the retrospective study protocol.

Clinical, Laboratory, and Sperm Preparation Protocols

All patients underwent evaluation of the uterine cavity with saline infusion sonogram before ovarian stimulation (12). Ovarian stimulation, hCG trigger, oocyte retrieval, embryo culture, and ET were carried out based on previously described protocols (12). Gonadotropin dosing for ovarian stimulation was based on patient age, body mass index (BMI, in kilograms per meter squared), antral follicle count, and serum antimüllerian hormone level. Patients requiring pretreatment before ovarian stimulation were started on either 0.1-mg E_2 patches (Vivelle-Dot estradiol transdermal system, Novartis Pharmaceuticals Corporation) or oral contraceptive (OC) pills (ORTHO-NOVUM 1 mg norethindrone and 0.035 mg ethinyl estradiol, Ortho-McNeil-Janssen Pharmaceuticals, Inc.) in the preceding luteal phase. Patients received OC pills for 10–14 days for luteal pretreatment and patients on an extended course of OC pills before ovarian stimulation were excluded from the analysis.

Ovarian stimulation was performed with gonadotropins (Follistim, Merck; Gonal-F, EMD-Serono Inc.; and Menopur, Ferring Pharmaceuticals Inc.), with ovulation being suppressed with once daily 0.25 mg ganirelix acetate (Merck) injections based on a previously described flexible protocol (13). hCG (Novarel, Ferring Pharmaceuticals Inc. or Pregnyl, Merck) was used as the ovulation trigger. In general, the hCG trigger was administered when the two lead follicles attained a mean diameter >17 mm and according to a sliding scale (10,000 IU for E_2 <1,500 pg/mL, 5,000 IU for E_2 1,501–2,500 pg/mL, 4,000 IU for E_2 2,501–3,000 pg/mL, and 3,300 IU for E_2 >3,001 pg/mL). Oocyte retrieval was performed 34–35 hours after hCG administration under transvaginal ultrasound guidance with conscious sedation. Intramuscular P (50 mg daily) was begun the day after oocyte retrieval for luteal support in all patients, irrespective of the hCG trigger dose (12).

Semen samples produced on the day of oocyte retrieval were evaluated for volume, count, concentration, and motility using World Health Organization criteria (14). Fertilization of oocytes was carried out with either conventional in vitro insemination or intracytoplasmic sperm injection (ICSI), depending on the semen sample and the couple's reproductive history (15). Oocytes were examined 12–17 hours after insemination or sperm injection for fertilization and the resulting embryos were incubated in in-house culture media (15). Cleavage-stage embryos were graded based on the Veeck criteria (16). All fresh ETs were performed on day 3 with Wallace catheters (Smiths Medical Inc.). No significant changes occurred in laboratory conditions, culturing, or ET technique during the study period. Embryos that were taken to biopsy for preimplantation genetic diagnosis or screening were excluded.

Study Variables

Demographic and baseline characteristics recorded for each patient included age, gravidity, parity, BMI (in kilograms per meter squared), infertility diagnosis, cycle day 2/3 antimüllerian hormone (in nanograms per milliliter) level, and cycle day 2/3 FSH (in milliinternational units per milliliter) level. Ovarian stimulation parameters recorded were total days of ovarian stimulation, total days of GnRH-a administration, total dosage of gonadotropins administered (in international units), E_2 level (in pictograms per milliliter) on the day of trigger, peak endometrial thickness (in millimeters), total number of oocytes retrieved, and mature oocytes. The percentage of ICSI cycles, fertilization rate (%), and supernumerary embryos available for cryopreservation was also recorded. The pregnancy outcomes assessed after day 3 ET included biochemical pregnancy, clinical pregnancy, spontaneous miscarriage, and live birth rates. A biochemical pregnancy was defined as positive hCG without a gestational sac. Clinical PR was defined as the number of intrauterine gestations with fetal cardiac activity per IVF-ET cycle. Any pregnancy loss after visualization of an intrauterine gestation was considered a spontaneous miscarriage and any birth after 24 weeks of gestation was considered a live birth.