Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovarian stimulation for in vitro fertilization and vitrified embryo transfer cycles

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Objective: To assess live-birth defects after a luteal-phase ovarian-stimulation regimen (LPS) for in vitro fertilization (IVF) and vitrified embryo transfer (ET) cycles.
Design: Retrospective cohort study.
Setting: Tertiary-care academic medical center.
Patient(s): Infants who were born between January 1, 2013 and May 1, 2014 from IVF with intracytoplasmic sperm injection (ICSI) treatments (n = 2,060) after either LPS (n = 587), the standard gonadotropin-releasing hormone–agonist (GnRH-a) short protocol (n = 1,257), or mild ovarian stimulation (n = 216).
Intervention(s): The three ovarian-stimulation protocols described and assisted reproductive technology (ART) treatment (IVF or ICSI, and vitrified ET) in ordinary practice.
Main Outcome Measure(s): The main measures were: gestational age, birth weight and length, multiple delivery, early neonatal mortality, and birth defects. Associations were assessed using logistic regression by adjusting for confounding factors.
Result(s): The final sample included 2,060 live-born infants, corresponding to 1,622 frozen–thawed (FET) cycles, which led to: 587 live-born infants from LPS (458 FET cycles); 1,257 live-born infants from the short protocol (984 FET cycles); and 216 live-born infants from mild ovarian stimulation (180 FET cycles). Birth characteristics regarding gestational age, birth weight and length, multiple delivery, and early neonatal death were comparable in all groups. The incidence of live-birth defects among the LPS group (1.02%) and the short GnRH-a protocol group (0.64%) was slightly higher than in the mild ovarian-stimulation group (0.46%). However, none of these differences reached statistical significance. For congenital malformations, the risk significantly increased for the infertility-duration factor and multiple births; the adjusted odds ratios were 1.161 (95% confidence interval [CI]: 1.009–1.335) and 3.899 (95% CI: 1.179–12.896), respectively. No associations were found between congenital birth defects and various ovarian-stimulation regimens, maternal age, body mass index, parity, insemination method, or infant gender.
Conclusion(s): To date, the data do not indicate an elevated rate of abnormality at birth after LPS, but further study with larger populations is needed to confirm these results. However, infertility itself poses a risk factor for congenital malformation. A higher likelihood of birth defects in multiple births may lead couples to favor elective, single ET; couples undertaking ART should be made aware of the known increased birth defects associated with a twin birth. (Fertil Steril® 2015;103:1194–201. ©2015 by American Society for Reproductive Medicine.)
Key Words: Luteal phase ovarian stimulation, in vitro fertilization, intracytoplasmic sperm injection, live birth, frozen embryo transfer, congenital malformation

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Since the first live birth resulting from in vitro fertilization (IVF) in the United Kingdom in 1978 (1), IVF has become a major alternative in the treatment of infertile couples. The number of infants born as a result of this technology has risen rapidly. According to a report from a 2009 survey on assisted reproductive technology (ART) in Europe, a total of 399,020 ART cycles were performed in a population of 373.8 million, corresponding to 1,067 cycles per million inhabitants (2), and this proportion may be increasing every year.

Numerous studies have explored the type and incidence of ART-related side effects in women who use these fertility services, and the potential impact on their offspring. Although IVF complication rates seem to be low (3), concern is still increasing about risks regarding this treatment procedure, e.g., suboptimal oocyte or embryo quality induced by premature luteinization (4), ovarian hyperstimulation syndrome (OHSS), and thromboembolism after hormonal stimulation, and infection and abdominal bleeding caused by egg collection (3). Therefore, influential innovations in stimulation regimens have been an integral part of IVF treatment for the past 30 years. However, these innovations have always limited ovarian stimulation initiation to the early follicular phase of the menstrual cycle, which may have elicited a premature luteinizing hormone (LH) surge, with multiple follicular development stimulated by exogenous gonadotropin. Consequently, the question of how to effectively suppress premature LH surge has traditionally been a researcher obsession.

To circumvent the premature LH surge obstacle, researchers have designed numerous stimulation regimens, ranging from pituitary down-regulation technology (beginning in the early 1980s) (5) to aggressive stimulation in combination with a gonadotropin-releasing hormone (GnRH) antagonist (during the past decade) (6). These solutions make stimulation complex and make complications caused by OHSS, which vary from mild to extremely severe illness, into rare but potentially life-threatening conditions.

In 2009, a 40-year-old woman with a 10-year history of primary infertility became pregnant with a twin pregnancy after accidental luteal-phase ovarian stimulation (LPS) at our center, and had a favorable delivery (7). This case paved the way to the possibility of successful outcomes with LPS. We investigated 242 women who received LPS (Supplemental Fig. 1, available online).

A satisfactory clinical pregnancy rate of 55.46% was obtained, resulting in 68 live births and 44 ongoing pregnancies at that time. Moreover, no premature LH surges occurred, nor did moderate-to-severe OHSS during the stimulation. The study proved that LPS is feasible for producing competent oocytes and/or embryos with optimal pregnancy outcomes (8). To date, this unique approach has resulted in hundreds of infants born after embryo vitrification.

Accompanying the desire to continuously optimize ovarian stimulation is a concern about whether LPS is safe as a baby grows into childhood and adulthood. Today, GnRH-a regimens using exogenous gonadotropins, which were found to cause no greater incidence of bodily malformations than that expected in the general population (9), are still the most frequently applied ovarian-stimulation approaches worldwide. They appear to be safe for the offspring who originate from this regimen.

The mild ovarian-stimulation approach administers either lower doses (over fewer days) of exogenous gonadotropins, or other compounds (such as antiestrogens, aromatase inhibitors, or GnRH-antagonist), to limit the number of oocytes obtained for IVF to <7 (10). This regimen can reduce patient discomfort and risk, and lower the duration and intensity of the pharmacologic interventions (11). Thus, mild stimulation may interfere less with normal ovarian physiology and result in better oocyte and/or embryo quality with reduced aneuploidy in the human preimplantation embryo (12). In consideration of their safety statistics for offspring, we selected the standard GnRH-a short protocol, and the mild ovarian-stimulation approach, to be used in the control groups, to evaluate the safety for offspring born from IVF and vitrified embryo transfer (ET) after LPS.

MATERIALS AND METHODS

Study Population and Design

A retrospective cohort study was conducted at the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine (Shanghai, People's Republic of China). The study was approved by the hospital's ethics committee. Infertile couples, who underwent IVF or intracytoplasmic sperm injection (ICSI) treatment with frozen and then thawed embryo transfer (FET) using LPS, the standard GnRH-a short protocol, or the mild ovarian-stimulation regimen, were recruited at our center. Informed written consent was obtained from patients in accordance with the ethics committee protocol.

These patients underwent the procedures from March 1, 2012 to July 1, 2013, leading to births between January 1, 2013 and May 1, 2014. Infants born to mothers with reported maternal diseases, such as gestational diabetes mellitus (13, 14), hypertension (15), and thyroid disorders (16, 17), or adverse environmental exposure (18–22) during pregnancy, were excluded from this analysis because of the possible association of these factors with birth defects. The final data, involving 2,060 live-born infants, delivered after IVF with ICSI and FET, were stratified into groups according to the method of ovarian stimulation: 587 births after LPS, 1,257 births after the standard GnRH-a short protocol, and 216 births after mild ovarian stimulation. The study design and participant selection procedure are presented in Supplemental Figure 2 (available online).

Treatment

The details of the ovarian-stimulation regimen for LPS are extensively described elsewhere (Supplemental Fig. 1) (8). Briefly, ovarian stimulation was conducted for patients with antral follicles <8 mm on days 1–3 after ovulation, by injecting 225 IU of hMG (Anhui Fengyuan Pharmaceutical Co. Ltd) and simultaneously administering 2.5 mg of letrozole (Jiangsu Hengrui Medicine Co. Ltd) every day. Daily administration of 10 mg of medroxyprogesterone acetate was added