Is frozen embryo transfer cycle associated with a significantly lower incidence of ectopic pregnancy? An analysis of more than 30,000 cycles

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Objective: To analyze the incidence of ectopic pregnancy (EP) in fresh compared with frozen-thawed cycles.
Design: Retrospective cohort study.
Setting: Teaching hospital.
Patient(s): Thirty-one thousand nine hundred twenty-five women undergoing in vitro fertilization–embryo transfer (IVF-ET) from January 2006 to December 2013.
Intervention(s): Fresh IVF-ET compared with frozen-thawed ET (FET).
Main Outcome Measure(s): Incidence of EP with fresh IVF-ET compared with frozen-thawed ET cycles, clinical pregnancy rate, and rate of EP per clinical pregnancy.
Result(s): For the fresh IVF cycles, 19,173 patients underwent oocyte retrieval; 15,042 had an ET, 6,431 of these patients (42.7%) had a clinical pregnancy, and among these 297 (1.97%) appeared to have an EP. The group of patients undergoing frozen-thawed ET (12,752 patients) included 12,255; there were 5,564 pregnancies (45.4%) and 124 ectopic implants (1.01%). The incidence of an EP per clinical pregnancy was 4.62% for the fresh transfer group compared with 2.22% for the frozen-thawed cycle group; this difference was statistically significant. In addition, the fresh ET cycles had the highest risk of EP, followed by day-3 embryo FET cycles; blastocyst FET cycles had the lowest risk of EP, and the differences were all statistically significant.
Conclusion(s): Frozen-thawed ET cycles were associated with a statistically significantly lower risk of EP when compared with fresh cycles. These findings are consistent with ovarian stimulation being associated with an increased risk of EP. (Fertil Steril® 2014;102:1345–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: Ectopic pregnancy, embryo cryopreservation, fresh cycle, frozen-thawed ET, ovarian stimulation

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An ectopic pregnancy (EP) is defined as a pregnancy implanted outside of the uterine cavity. Over 98% of EPs implant within the fallopian tubes (1, 2), commonly referred to as a tubal pregnancy. In vitro fertilization–embryo transfer (IVF-ET) is one of the major risk factors for an EP (3, 4). In fact, the first IVF treatment resulted in an EP (5). The reason why this pathology remains a common association of IVF is unclear (6). After IVF, embryos are transferred directly into the uterine cavity, and this process associated with assisted reproduction techniques (ART) would actually seem to reduce the risk of an EP. However, a significant number of ectopic pregnancies still occur. Reported rates of EPs in women undergoing IVF range from 2% to 5% (4, 6), which is higher than the rate among spontaneous pregnancies at 1%–2% (7, 8). Some of the hypotheses reported to explain the increased risk for EP associated with ART are tubal disease (9, 10), increased

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uterine contractions due to ovarian stimulation (11, 12), and dysfunction of the uterine musculature due to high progesterone levels (13).

Recent research has suggested that frozen-thawed ET (FET) is associated with a greatly reduced incidence of EP compared with fresh transfers (14, 15). However, ART data from clinics in Belgium from 2002–2012 reported no statistically significant difference in the incidence of EP in comparisons between fresh IVF cycles and frozen-thawed cycles (16). Therefore, further study is needed to determine whether FET is associated with a different EP risk compared with fresh cycles. If the risk for EP is reduced with FET embryos, cryopreservation might also reduce the risks associated with ovarian hyperstimulation. We retrospectively analyzed the data from an IVF center in the People's Republic of China from January 2006 to December 2013 to determine whether FET was associated with a significantly lower risk for EP compared with fresh cycles.

MATERIALS AND METHODS

This was a noninterventional, retrospective, single-center cohort study of patients in a routine clinical practice. To reflect the broad range of patients typically encountered in this clinical practice, no inclusion/exclusion criteria were applied to the baseline characteristics. Patients were treated at the Reproductive Medicine Center of Tongji Hospital from January 2006 to December 2013. A total of 31,925 patients were enrolled, and all patients gave written informed consent. Institutional review board approval was not required because all patients in this study underwent routine long gonadotropin-releasing hormone (GnRH) agonist IVF-ET clinical treatment at the center, and no additional intervention was performed.

All patients participating in fresh cycles underwent controlled ovarian stimulation according to the routine long GnRH agonist protocol. Pituitary suppression was achieved by daily subcutaneous injection of triptorelin acetate (Decapeptyl; Ferring) starting at the midluteal phase of the preceding cycle. When complete pituitary desensitization was confirmed by a low plasma estradiol (E_2) level of ~30 pg/mL and a luteinizing hormone (LH) level of ~2 mIU/mL, ovarian stimulation was started with the administration of recombinant follicle-stimulating hormone (FSH) (Gonal F, Serono; or Puregon, Schering-Plough). Recombinant human chorionic gonadotropin (hCG) (250 mg; Ovidrel; Serono) was given to trigger ovulation when two leading follicles reached a mean diameter of 18 mm. Oocytes were retrieved transvaginally 34 to 36 hours after hCG administration.

Fertilization of the oocytes took place either by IVF or intracytoplasmic sperm injection (ICSI), according to the sperm quality. The methods for sperm preparation, IVF, and embryo culture have been described previously elsewhere (17). Briefly, semen was collected in sterile containers by masturbation after 3 to 5 days of sexual abstinence and then was maintained at 37°C for 30 minutes. After liquefaction, the samples were analyzed for sperm concentration, motility, and morphology according to World Health Organization criteria (18). The oocytes were incubated in G-IVF medium (Vitrolife) and fertilized 3 to 4 hours after retrieval. Normally, fertilized oocytes were continuously cultured in G1 medium for 2 more days. Usually fewer than two best-quality embryos were transferred on day 3 after oocyte retrieval, according to the protocol developed by Chinese legislation. The additional good-quality embryos or blastocysts were cryopreserved for subsequent FET cycles (by slow freezing). From 2009 onward, vitrification was used for embryo cryopreservation at this center.

The FET cycles were from both natural cycles after spontaneous ovulation and hormone replacement treatment (HT) cycles. For the natural cycles, transvaginal ultrasound scans and measurement of the serum progesterone levels was initiated from cycle days 10–12 to assess endometrial thickness, follicle growth, and ovulation. Frozen-thawed ET was planned for 3 days after ovulation. Progesterone administration was started for luteal support from 1 day after ovulation. For the HT cycles, oral estradiol (Progynova; Bayer) was provided, 2 mg/day from cycle days 1–4, 4 mg/day from days 5–8, and 6 mg/day from days 9–12. Transvaginal ultrasound scanning was performed to assess the endometrial thickness and ovulation from day 13; the estradiol dosage was adjusted based on the endometrial thickness. We administered 40 mg of progesterone intramuscularly when the endometrium reached a thickness of 8 mm or maximum. Administration of 60, 80, or 80 mg of progesterone was provided for the following 3 days. Embryo transfer was performed on day 4, after 3 days of progesterone administration.

Serum hCG was measured to diagnose a pregnancy 2 weeks after ET and then was tested serially to monitor rising titers. A clinical pregnancy was defined as the presence of a gestational sac with fetal heart activity observed on ultrasound examination 5 weeks after oocyte retrieval (19). An EP was defined when a pregnancy was determined and accompanied by sonographic visualization of an extrauterine gestational sac (including any heterotopic gestations) or with an empty uterine cavity and increasing hCG levels (20).

All data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 13.0 (IBM). The data were analyzed to compare fresh cycles with FET cycles. For the FET group, the data from day-3 ET were compared with the blastocyst transfer group and analyzed. For the day-3 FET cycles, the difference between the two methods of ET was also analyzed. The differences in outcomes between the two groups were analyzed using chi-square tests. $P < .05$ was considered statistically significant.

RESULTS

From January 1, 2006, to December 2013, 19,173 fresh cycles were included in the study, and 258,625 oocytes were retrieved. The overall clinical pregnancy rate (PR) per oocyte retrieval for this 8-year period was 33.5%, and the PR per transfer was 42.7% (Table 1). The etiology of infertility for these pregnancies included tubal factors (61.5%), ovarian factors (4.2%), endometriosis (2.4%), male-factor infertility (23.8%), and others. There were 297 EPs (1.97%) that occurred after the transfer cycles. During the same period, a total of 12,752 FET cycles were enrolled. The PR of the FET cycles was 45.4% per ET, which was statistically significantly higher