REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

The association between polycystic ovary syndrome and ectopic pregnancy after in vitro fertilization and embryo transfer

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OBJECTIVE: We sought to assess the association between polycystic ovary syndrome (PCOS) and ectopic pregnancy after in vitro fertilization—embryo transfer (ET).

STUDY DESIGN: In this retrospective cohort study, we included 5339 women who had clinical pregnancies after in vitro fertilization treatment (PCOS, 205 women; non-PCOS, 5134 women) at Nanjing Medical University (China) between 2007 and 2011. Fresh and cryo-thawed ET cycles were analyzed respectively. The primary outcome measure was the occurrence of ectopic pregnancy. Multivariate logistic regression analysis was used to adjust for important confounders.

RESULTS: In fresh ET cycles of women who were undergoing controlled ovarian hyperstimulation (COH; n = 3303), women with PCOS had 3.06 times higher risk of ectopic pregnancy compared with those without PCOS (7.0% vs 2.4%; adjusted odds ratio [aOR], 3.06; 95% confidence interval [CI], 1.34—6.96). In the stratified analysis, for women without PCOS, the high estradiol group (>4085 pg/mL) had higher ectopic pregnancy rates compared with the low estradiol group (≤4085 pg/mL; 3.4% vs 2.0%; aOR, 1.99; 95% CI, 1.19—3.35); however, for women with PCOS, both high and low estradiol groups had high ectopic pregnancy rates (5.6% vs 7.7%; aOR, 0.92; 95% CI, 0.15—5.67). In cryo-thawed ET cycles without COH (n = 2036), the ectopic rates between women with and without PCOS were similar (2.2% vs 2.0%; aOR, 0.94; 95% CI, 0.22—4.07).

CONCLUSION: PCOS was associated with an increased risk of ectopic pregnancy after COH in fresh ET cycles, but not in cryo-thawed ET cycles. A possible explanation is that, compared with women without PCOS, women with PCOS appear to hold a lower threshold of hyperphysiologic estradiol level that triggers the occurrence of ectopic pregnancy after COH.

Key words: ectopic pregnancy, estradiol, IVF-ET, polycystic ovary syndrome, risk

Cite this article as: Wang J, Wei Y, Diao F, et al. The association between polycystic ovary syndrome and ectopic pregnancy after in vitro fertilization and embryo transfer. Am J Obstet Gynecol 2013;209:139.e1-9.

Ectopic pregnancy (EP) is a known complication of in vitro fertilization (IVF). The reported incidence of EPs after IVF varies from 2.1-8.6% of all clinical pregnancies,[1,2] which is higher than the estimated EP rate of 1.97 per 100 pregnancies among the general population in the United States[3] and the 1.0 per 100 pregnancies incidence in China. Abnormal estradiol and/or progesterone milieu has been proposed as a risk factor for EP[4-6]; during IVF treatment, hyperphysiologic hormonal levels, which are associated with controlled ovarian hyperstimulation (COH), have been linked to an increased risk of EP.[7,8]

Polycystic ovary syndrome (PCOS) is a common disorder that is associated with infertility in women who undergo IVF treatment and is characterized by ovulatory dysfunction and endocrine disorders such as hyperandrogenism.[9] In IVF cycles, women with PCOS are highly sensitive to medication during COH[10] and exhibit possibly higher estradiol and progesterone levels on the day of human chorionic gonadotropin (hCG) administration compared with women without PCOS,[11] which suggests that they might be at an increased risk of EP.

Abundant literature has reported an increased risk of pregnancy complications in women with PCOS after both natural conception and assisted reproductive technologies, which include miscarriage, preeclampsia, very preterm birth, gestational diabetes mellitus,

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Received Feb. 13, 2013; revised April 5, 2013; accepted May 1, 2013.

Supported by research grant number 2012CB944902 from the National 973 Program of China and grant number 81070465 from the National Natural Science Foundation of China.

The authors report no conflict of interest.

Presented, in part, in oral format at the 5th World Congress on Mild Approaches In Assisted Reproduction, Copenhagen, Denmark, May 4-6, 2012.

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0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2013.05.007

meconium aspiration, and large for gestational age independent of assisted reproductive technologies.[12] However, with regard to EP, the clear association between PCOS and EP after IVF has not been reported yet, although some studies mentioned EP rates of women with PCOS who conceived after different assisted reproductive technologies treatment modalities. The reported rates are inconsistent and vary from 0-10%[13-22] because of different treatment and grouping methods that have been used.

The purpose of this study was to analyze the possible association between PCOS and EP among clinical pregnancies that are achieved by fresh and cryo-thawed IVF cycles. If the association exists, we also aimed to assess its possible cause.

Materials and Methods

This study was a retrospective cohort analysis of women who achieved clinical pregnancies after IVF-ET in the Clinical Center for Reproductive Medicine, First Affiliated Hospital of Nanjing Medical University between January 2007 and December 2011. Data for individuals who started IVF treatment in our clinical center have been captured routinely in the Database of Clinical Center of Reproductive Medicine since 2006. The database includes the detailed information on patients' demographic and baseline characteristics, medical history, infertility-associated disorders such as PCOS, data of IVF procedure, and follow-up pregnancy outcomes. With access to the database with a unique treatment identification number for each patient, trained nurses collected the patient's medical and treatment information continuously along with the IVF procedure, until each embryo transfer (ET) procedure ended with a follow-up pregnancy outcome.

PCOS was diagnosed based on the Rotterdam criteria,[23] which means the fulfilment of 2 of the 3 diagnosis criteria (presence of oligoovulation/anovulation, polycystic ovaries, and excess adrogen activity) and excluding other diseases that would represent these.

During the study period, 15,924 ET cycles were performed. The overall implantation rate, clinical pregnancy rate, and live birth rate were 27.9% (8263/29,638), 41.9% (6675/15,924) and 35.2% (5613/15,924) per ET, respectively. Of these ET cycles, 6675 resulted in pregnancies. To ensure no duplication of data from the same patient who underwent multiple treatment cycles, only cycles that resulted in the first clinical pregnancy during the study period were included. Because embryo implantation potential affected EP occurrence,[1] pregnancies that resulted from donated oocytes or sperm were excluded from the analysis. Moreover, cycles that involved preimplantation genetic diagnosis or in vitro maturation were excluded. All patients who were included were Chinese. Fresh and cryo-thawed ET cycles were analyzed separately. For fresh ET cycles, to avoid interference by cryopreservation, cycles with cryopreserved oocytes or sperm were excluded. Additionally, to eliminate the bias caused by treatment, natural cycles (n = 58) and mild stimulation cycles (n = 166) were excluded from the fresh ET cycles. Thus, the final study population consisted of 5339 women who achieved clinical pregnancies. These women were grouped by diagnosis of PCOS into PCOS and non-PCOS cohorts in fresh and frozen-thawed cycles respectively.

The primary outcome measure was the occurrence of EP, which was diagnosed by ultrasound examination or laparoscopic surgery visualizing $\geq$1 gestational sacs outside the uterus or by abnormally increasing serum hCG level without sonographic visualization and the absence of chorionic villi inside the uterus after uterine curettage, which was treated by methotrexate. A *clinical pregnancy* was defined as the ultrasound observation of $\geq$1 gestational sac at 6 weeks after ET or diagnosis of an EP. A clinical intrauterine pregnancy was diagnosed as a pregnancy with $\geq$1 gestational sacs detected within the uterus cavity. *Heterotopic pregnancy* was defined when fetal heart beat was found at both intrauterine and ectopic sites. All EPs were followed until a urine hCG test was negative after treatment. In our study, either ectopic or heterotopic pregnancy was categorized as EP. The EP rate was calculated by dividing EPs by the total number of clinical pregnancies (sum of ectopic and clinical intrauterine pregnancies).

In fresh ET cycles, all cycles were treated with COH, under which 3 standard regimens applied: gonadotropin-releasing hormone—agonist long protocol (73%), gonadotropin-releasing hormone—agonist short protocol (20%), or gonadotropin-releasing hormone—antagonist protocol (7%). In frozen-thawed ET cycles, COH was not performed; instead, 3 methods of endometrial preparation were carried out that included natural (44%), artificial (19%), and mild stimulation (37%) protocol. Mild stimulation refers to ovarian stimulation with the use of clomiphene citrate or letrozole and subsequently the administration of human menopausal gonadotropin or not, depending on follicle growth. *Good-quality embryos* were defined as embryos with a normal cleavage rate and $\leq$10% fragmentation. The embryos were transferred with the Cook Sydney IVF ET catheter (K-Jets-7019-SIVF; Cook IVF, Eight Miles Plains, Queensland, Australia) and placed 1.5-2 cm below the fundus under ultrasound guidance.

Approval from the institutional review board was not required because our center has been licensed by the Ministry of Public Health of People's Republic of China since 2001; this was a retrospective study with no specific clinical intervention on IVF treatment.

For univariate analysis of clinical variables and the outcome measures, 2-sample *t* tests, 2-sample Wilcoxon tests, χ^2, or Fisher exact test were used where appropriate. To estimate the independent association between PCOS and EP with the adjustment of important confounders, multivariate logistic regression models were used. Considering different features in fresh and frozen-thawed ET cycles, 2 independent regression models were constructed. Based on published findings, the confounding variables included previous EPs,[24] tubal factor infertility, endometriosis, male factor infertility, other infertility factors, number of embryos transferred,[1,2] endometrial thickness,[25] days of stimulation, gonadotropins dosage, ovarian