Ectopic pregnancy rate increases with the number of retrieved oocytes in autologous in vitro fertilization with non-tubal infertility but not donor/recipient cycles: an analysis of 109,140 clinical pregnancies from the Society for Assisted Reproductive Technology registry

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Objective: To study the impact of controlled ovarian stimulation on ectopic pregnancy (EP) rate as a function of the number of oocytes retrieved, using donor IVF cycles as a control.
Design: Retrospective cohort study using a large national database.
Setting: Not applicable.
Patient(s): Data from 109,140 cycles from the 2008–2010 SART registry, including 91,504 autologous cycles and 17,636 donor cycles in patients with non-tubal infertility.
Intervention(s): Varying amounts of oocytes retrieved in autologous and donor IVF.
Main Outcome Measure(s): Ectopic pregnancy rates.
Result(s): In autologous cycles, the EP rate significantly increased as oocyte yield increased. This association was not found in oocyte recipients.
Conclusion(s): In autologous IVF cycles, increasing oocyte yield is correlated with a significantly increased EP rate. This association is not found in oocyte recipients, indicating that the increased EP rate may be due to the supra-physiologic hormone levels achieved with controlled ovarian hyperstimulation. (Fertil Steril® 2015;104:873–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Ectopic pregnancy, in vitro fertilization, IVF, autologous, donor, oocytes

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Ectopic pregnancy (EP) (1) is a serious potential complication of IVF, and recent efforts have focused on identifying intrinsic and modifiable risk factors for EP in the infertile population (2–4). Although the rate of EP is <2% in the general population, it ranges from 2% to 11%

of pregnancies resulting from IVF (4). One hypothesis for this increased rate of EP is the inherent biologic differences in the infertile population (for example, increased rates of tubal factor in the population requiring IVF); other studies postulate that this increased rate is due in part to the supraphysiologic hormonal milieu resulting from ovarian stimulation, which has been shown to alter gene activation, angiogenesis, and even placentation (5–8).

Many recent studies have been aimed at identifying modifiable risk factors in IVF to decrease EP rates. Studies have shown that factors associated with lower EP rates include lower number of embryos transferred, lower volume of transfer fluid (9), deep fundal ET (10), day-5 blastocyst transfer (11), frozen embryo transfer (FET) (12, 13), and donor IVF (14). A recent extensive review by Perkins et al. (3) at the Centers for Disease Control and Prevention showed higher rates of EP in fresh non-donor cycles, Asian and African American patients, patients with tubal factor infertility, patients with endometriosis, and in uterine factor infertility. The main modifiable risk factor identified was the number of embryos transferred, showing a dose–response curve for higher EP rates with two or more embryos transferred. Other weaker associations included assisted hatching, conventional IVF without intracytoplasmic sperm injection, higher FSH dosage, and age >30 years. The predominant hypothesis is that EP rates are lower with FET and donor IVF cycles because these types of IVF involve placing an embryo into a more "natural" endometrium: a nonstimulated environment and a more physiologic hormonal milieu. This hypothesis is supported by studies of patients with polycystic ovary syndrome (PCOS). The EP rate after fresh embryo transfer is significantly higher than in patients without PCOS (15), but this is mitigated when FET is used, supporting the hypothesis that the supraphysiologic hormonal milieu in fresh autologous embryo transfer, which is likely to be even higher in PCOS patients, contributes to the EP rate. It stands to reason that, if modifiable risk factors can be identified and avoided, these safer techniques could be offered as first-line treatments and can be encouraged, especially in patients at higher risk for EP. These patients may include those patients with PCOS, those with high hormone levels at the time of trigger, previous ectopic pregnancies or known tubal factor infertility, extremes of age, or heavy smokers.

No study to date has focused primarily on the rate of EP as related to the number of oocytes retrieved in autologous cycles. We hypothesized that, using the number of oocytes retrieved as a representation of supraphysiologic hormonal status, we would find higher rates of EP in patients with a higher number of oocytes retrieved in autologous IVF cycles. We performed a separate analysis in donor IVF cycles for comparison, because the uterine environment in the embryo recipient is not exposed to such supraphysiologic hormone levels. We hypothesized that there would be no effect of number of oocytes retrieved on the EP rates in the donor cycles.

MATERIALS AND METHODS

The primary objective of this study was to determine whether IVF cycles in which a higher number of oocytes were retrieved are also those cycles more likely to result in an EP. Institutional review board approval was granted from the Duke Medicine Institutional Review Board for this retrospective cohort study. The Society for Assisted Reproductive Technology (SART) database from 2008–2010 was analyzed. All cycles in patients with the diagnosis of tubal factor infertility were excluded. We further excluded cycles for which the type of IVF (donor vs. autologous), the number of oocytes retrieved, or the cycle outcome was not listed. The data were analyzed by division into fresh autologous cycles and donor IVF cycles, and donor cycles were used for comparison. In both cohorts we grouped the cycles into subcategorical bins based on the number of oocytes retrieved, using the categories of 0–5, 6–10, 11–15, 16–20, 21–25, and >25 oocytes retrieved, consistent with previous literature (16). Demographic information was extracted for both cohorts, including patient age, maximum FSH levels, smoking status, and total FSH dose during the IVF cycle. We then calculated the average number of oocytes retrieved per category and the percentage of ectopic pregnancies per category. We performed linear regression using the average number of oocytes per category and the EP percentage per category. This was performed separately for autologous and donor cycles. We defined "clinical pregnancies" as including intrauterine, ectopic, and heterotopic pregnancies. For the purpose of our study we grouped ectopic pregnancies and heterotopic pregnancies together as "ectopic pregnancy." All statistical analyses were carried out using the R statistical package (17).

To control for the confounding effect of the number of embryos transferred on EP rates, we performed a sensitivity analysis in which we accounted for the number reported for "fresh embryos to uterus" in the analysis. We again performed linear regression, this time calculating the *P* value by accounting for the embryos transferred in the calculation. We also compared EP rates in cleavage vs. blastocyst transfers; this was calculated by the number of EPs in all cycles listed as blastocyst transfer and all cycles listed as cleavage transfer, divided by the clinical pregnancies in those categories. We excluded all cycles in which the type of transfer (blastocyst vs. cleavage) was not listed. We performed this same calculation using only cycles in which two embryos were transferred, to correct for the fact that cleavage transfers more often transfer two embryos, whereas blastocyst transfers are more likely to transfer only one.

RESULTS

A total of 109,140 clinical pregnancies were included in our analysis. This encompassed 91,504 clinical pregnancies resulting from autologous IVF and 17,636 clinical pregnancies resulting from donor/recipient IVF cycles. The patient demographics followed expected patterns (Table 1). There seems to be an inverse correlation between patient age and number of oocytes retrieved in the autologous population, with older patients producing lower oocyte yields. This correlated with the mean FSH dose, which was higher (indicating less ovarian reserve) in the autologous cycles in which fewer oocytes were retrieved. The FSH was significantly higher in the patients undergoing oocyte recipient cycles. The percentage of