Ectopic pregnancy rates after in vitro fertilization: a look at the donor egg population

In an 8-year review of ectopic pregnancy (EP) rates in donor egg recipients and standard patients undergoing in vitro fertilization–embryo transfer (IVF-ET) at a large university-based program, we report an EP rate of 0.6% in donor egg recipients and 0.9% in standard IVF patients, a difference that is not statistically significant. Donor egg recipients were found to have a significantly lower incidence of tubal disease compared with standard IVF patients; however, tubal disease was not found to be an independent risk factor for EP in our practice, perhaps owing to aggressive management of tubal disease. (Fertil Steril® 2009;92:1791–3. ©2009 by American Society for Reproductive Medicine.)

The use of donor eggs with in vitro fertilization (IVF) has become increasingly common and successful. It is typically used in patients with diminished ovarian reserve, ovarian failure, or genetic disorders such as Turner syndrome. The annual reports from the United States National Registry consistently demonstrate high pregnancy and delivery rates for oocyte donation cycles. Outcome data collected in 2006 from 426 fertility centers in the United States demonstrates a live birth rate of 53.7% per fresh embryo transfer (ET) when using donor oocytes, compared with a 35.4% live birth rate per fresh ET when using general IVF (1).

We sought to explore whether there was a difference in ectopic pregnancy (EP) rates between patients undergoing standard IVF and donor egg recipients. Ectopic pregnancy is estimated to occur in 2%–5% of clinical pregnancies after IVF (2–4). Risk factors identified for EP after IVF include tubal factor infertility (5–7) and technical aspects of IVF therapy, such as assisted hatching (8), frozen embryo transfer (6), higher transfer volume (9), deep fundal transfer (10, 11), and the practice of multiple embryo transfer (7). Tubal disease has been identified as one of the most significant risk factors for tubal pregnancy (5–7, 12). The incidence of tubal disease in the donor egg population is thought to be significantly lower than in the standard IVF population, although no further data is available on this topic. Therefore, donor egg recipients might benefit from lower EP rates compared with the standard IVF population.

In his study of ectopic pregnancy rates, Clayton et al. (7) reviewed population-based data of pregnancies conceived with assisted reproductive technologies (ART) in U.S. clinics between 1999 and 2001. He demonstrated a significantly lower EP rate in the fresh donor egg recipient population compared with the fresh nondonor IVF population (1.4% vs. 2.2%; odds ratio 0.63, 95% confidence interval 0.54–0.75). He also identified risk factors for EP, such as tubal factor infertility, endometriosis, and other nontubal female factors of infertility.

The objective of the present study was to compare rates of EP in fresh embryo transfers between nondonor IVF patients and donor egg recipients over a period of 8 years in one institution. We expected to observe lower EP rates among donor egg recipients compared with the standard IVF population. Additionally, overall EP rates in IVF were analyzed based on day of embryo transfer, because the decrease in uterine contractility reported on day 5 may have an effect on reducing the risk of tubal migration and subsequent EP (4, 13, 14).

The study was exempted from review by the New York University Institutional Review Board, because analysis involved preexisting deidentified data that precluded identification of individual patients. A retrospective analysis was performed using our program's database and records of clinical IVF and donor egg pregnancies established between 1998 and 2006. A total of 4,186 clinical pregnancies were identified from fresh ET in nondonor IVF patients, and 884 clinical pregnancies were identified from fresh ET in donor egg recipients. Clinical pregnancy was defined as the presence of at least one gestational sac visualized by transvaginal ultrasonography between cycle days 42 and 49. Ectopic pregnancy was defined as the presence of an extrauterine gestation documented by ultrasound or salpingectomy, and heterotopic pregnancy (HP) was defined as EP coexisting with a synchronous intrauterine pregnancy. These definitions are consistent with Society of Assisted Reproductive Technology (SART) guidelines for outcomes reporting.

Statistical analysis was performed at the NYU Department of Environmental Medicine, Division of Biostatistics. Patient and cycle characteristics were compared using Student's *t*-test and Wilcoxon rank sum test for continuous variables and χ^2 test for

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Received March 27, 2009; revised May 7, 2009; accepted May 18, 2009; published online June 13, 2009.
E.R. has nothing to disclose. D.K. has nothing to disclose. L.K. has nothing to disclose. M.L. has nothing to disclose. F.L. has nothing to disclose. J.G. has nothing to disclose.
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TABLE 1

Comparison of ectopic pregnancy rates in fresh nondonor versus fresh donor IVF-ET.

	Non donor IVF-ET (n = 4,186)	Donor IVF-ET (n = 884)	*P* value
Ectopic pregnancies/clinical pregnancies	37/4,186 (0.9%)	5/884 (0.6%)	NS
Mean age (yrs)	35.9	42.5	<.01
Tubal disease	20.7%	12.8%	<.01
Mean no. embryos transferred	2.94	2.3	<.01

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categorical variables. With categorical data that was exceptionally sparse, the Fisher exact test was used. A *P*-value of $\leq .05$ was considered to be statistically significant.

Of 4,186 clinical pregnancies in nondonor IVF patients, 37 (0.9%) were identified as EP or HP. Of these 37, 28 (76%) were EPs and 9 (24%) were HPs. Of the 884 clinical pregnancies in donor egg recipients, 5 (0.6%) were ectopic, representing a difference between the two groups that is not statistically significant ($P=.343$). The incidence of tubal disease was significantly lower in the donor egg recipients than in the standard IVF population (12.8% vs. 20.7%; $P<.01$). The mean age was 42.5 years in the donor egg recipient group and 35.9 years in the nondonor IVF group ($P<.01$). The mean number of embryos transfered in the donor egg recipients and in the nondonor IVF patients were 2.3 and 2.94, respectively ($P<.01$) (Table 1).

In the comparison of EP rates between day 3 and day 5 ET between 1998 and 2006 in the standard IVF population, we looked at a total of 4,186 pregnancies. Of 1,991 clinical pregnancies resulting from day 3 transfer, 8 (0.4%) were EPs. Of 2,195 clinical pregnancies resulting from day 5 transfer, 29 (1.3%) were EPs. This represents a statistically significant difference ($P=.002$).

A multivariate logistic regression analysis in R 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was performed to independently identify associations between maternal and ART factors that might have a direct effect on the incidence of EP rates. The model included patient age, number of embryos transfered, day of embryo transfer (day 3 vs. day 5), type of IVF (nondonor vs. donor), and infertility diagnosis subcategorized into tubal disease and nontubal female factors, including diminished ovarian reserve, endometriosis, uterine factor, polycystic ovary syndrome (PCOS), unexplained infertility, and other factors. Transfer volume remained consistent among embryo transfers at 15–20 μL medium, and frozen ETs were not included in our study population. Deep fundal transfer could not be adequately assessed as a variable, because not all transfers were performed under ultrasound guidance. Assisted hatching was performed only with day 3 transfers and was not included in the analysis.

As a result of the regression analysis, patient age ($P=.25$), number of embryos transfered ($P=.18$), type of IVF ($P=.94$) and infertility diagnosis of tubal disease ($P=.92$) were not statistically significant contributors to the incidence of EP in our practice. Factors such as day of ET ($P=.003$) and nontubal female factors of infertility ($P=.011$) were statistically significant contributors to the incidence of EP.

We observed a significantly lower incidence of EP overall in our practice compared with nationally reported EP rates in IVF. However, there was no statistical difference whether undergoing autologous IVF or IVF using donor eggs. Although donor egg recipients were found to have a significantly lower incidence of tubal disease compared with the standard IVF population, in our practice tubal disease was not an independent risk factor for EP, and this may reflect aggressive surgical management of tubal disease within a successful IVF program. Clayton et. al. (7) showed conflicting data; however, our sample size is considerably smaller and the power may not be sufficient to detect such small statistical differences.

Donor egg recipients were on average 6.5 years older than the patients in the nondonor group; however, age was not found to independently affect tubal pregnancy rates in our regression analysis nor in the literature (7). The number of embryos transfered was found to be slightly lower in the donor egg recipients (2.3 vs. 2.94; $P<.01$); however, it is unlikely that this small difference could have exerted an effect on EP rates, and this was confirmed in our regression analysis.

Over the 8-year period studied, the rate of EP in our center was 0.9% for autologous IVF and 0.6% for IVF with donor eggs. These rates are significantly lower than the national rate of 1.8% reported by SART/American Society for Reproductive Medicine for U.S. centers (3). These results also compare favorably to the estimated 2% incidence of EP in the U.S. (15).

Because our laboratory has been shifting toward the practice of implanting embryos at the blastocyst stage, we explored the subsequent effects on EP rates. We have already reported a slightly increasing EP trend that mirrors the shift to blastocyst transfer (16). In the comparison of EP rates between day 3 and day 5 ET, we found a statistically significant difference, with higher EP rates resulting from blastocyst transfer. This cannot be attributed to the number of embryos transfered, because the mean number transfered was significantly lower in day 5 cycles than in day 3 cycles (2.4 vs. 3.4; $P<.01$). Additionally, the incidence of tubal disease was similar between the two groups (20% vs. 18.8%; $P=.32$) and is therefore unlikely to be a confounder to the data. As mentioned above, transfer volume did not vary among ETs. Recent evidence has shown that the probability of live birth after fresh IVF is significantly higher after blastocyst-stage ET compared with cleavage-stage ET when equal numbers of embryos are transfered (17). The overall higher success rate of embryo implantation and subsequent pregnancy at the blastocyst stage may predict the higher EP rates seen in day 5 transfers.

In identifying independent risk factors for EP in our population, factors such as maternal age, number of embryos transfered, type of IVF, and history of tubal disease did not play a role in predisposition to EP. The literature has extensively suggested that the presence of damaged tubes does confer a higher risk for EP in IVF (5–7, 12). Although not examined in the present study, in our practice aggressive management of documented tubal disease with salpingectomy may help prevent EP after IVF. However, only a randomized controlled trial of salpingectomy in patients with diagnosed tubal disease can conclusively verify the merit of our clinical practice. The risk of EP was increased among women with nontubal female factors, such as endometriosis, uterine factor, PCOS, and other factors, and this is consistent with earlier studies (5, 7). One limitation to the present study was the lack of specific clinical data pertaining to earlier history of EP in our patients.

In summary, the present results suggest that in our practice, donor egg recipients have an EP risk similar to that in the general IVF population. We report an EP rate of 0.9% for standard IVF and 0.6% for donor egg recipients, both lower than nationally reported rates. Contrary to existing reports (4), a slightly higher risk of EP is seen with the shift to blastocyst transfer. With recent data showing an increase in successful implantation and clinical pregnancy at the blastocyst stage over the cleavage stage (17), this finding is likely to follow.

Acknowledgments: The authors thank Alan S. Berkeley, M.D., Lisa Kump, M.D., Nicole Noyes, M.D., and the embryology and nursing staff at the NYU Fertility Center for their assistance in data collection.

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