Is timing everything? Risk of ectopic pregnancy in day 3 versus day 5 transfer

Assisted reproductive technology (ART) is associated with an increased risk of ectopic pregnancy compared to the general population. While some of this risk is inherent to patient factors, such as tubal or uterine factor infertility or endometriosis, ART itself likely also contributes to an increased risk of ectopic pregnancy. As clinicians, we must understand these risks to fully counsel patients and work to minimize the risk of this life-threatening condition. Thankfully, ectopic pregnancy rates after in vitro fertilization cycles have decreased over time, from 2.0% in 2001 to 1.6% in 2011 (1). This decline is likely related to advances in embryo culture conditions and embryo selection, which have led to a practice shift favoring single embryo transfer. The risk of ectopic pregnancy in fresh donor egg cycles, in which single embryo transfer is recommended, is 1% compared to 2% in autologous transfers (1). Lower rates of ectopic pregnancy are likely also related to conventional practice favoring blastocyst over cleavage-stage transfers. The meta-analysis by Zhang et al. (2) found that a day 5 transfer was associated with a lower risk of ectopic pregnancy than a day 3 transfer (relative risk (RR) 0.67 for all transfers; RR 0.78 for fresh transfers; and RR 0.43 for frozen embryo transfers). However, this study was limited because it contained mostly retrospective studies and the few randomized controlled trials included had small sample sizes. Additionally, while most studies included controls for the number of embryos transferred, two studies did not.

Krishnamoorthy et al. (3) performed a Society for Assisted Reproductive Technology (SART) database review to determine if there is a difference in the ectopic pregnancy rates between day 3 and day 5 embryo transfers. They included 51,133 day 3 and 71,855 day 5 frozen embryo transfer cycles that resulted in clinical, ectopic, or heterotopic pregnancy. The incidence of ectopic pregnancy was 1.1% after day 3 transfers and 0.8% after day 5 transfers ($P>.001$). After controlling for age, BMI, smoking status, number of embryos transferred, and tubal factor infertility, the odds for ectopic pregnancy was 0.75 for day 5 transfers compared to day 3 transfers. Odds were unchanged when restricting to cycles in which 5 or fewer embryos were transferred (odds ratio, 0.75).

We applaud the investigators for their thorough review of this expansive data set and their insightful approach in answering this clinical question. By evaluating many cycles from a diverse pool of patients, they have offered more insight into reducing the risk of ectopic pregnancy in ART. The investigators wisely limited their analysis to frozen embryo transfers, controlling for the increased risk of ectopic pregnancy with fresh embryo transfer due to the altered hormonal milieu during ovarian hyperstimulation. Supraphysiologic estrogen levels may disrupt fallopian tube function, leading to an increase in ectopic pregnancies (4). Epidemiologic studies have shown a higher rate of ectopic pregnancy in fresh vs. frozen transfers (1.8% vs. 1.0%) (1), so we must interpret the data with that understanding.

Although this database study offers information on a large set of patients, a major limitation of a SART database study is the fidelity of the data given the variability in how clinics report demographic factors and cycle outcomes. In this study, a larger proportion of day 3 embryo transfer patients with ectopic pregnancy had an unknown smoking history than those in the day 5 group (45.0% vs. 11.4%). If more patients in the day 3 group were active smokers, this known ectopic risk factor could be a potential confounder leading to an increased incidence of ectopic pregnancy in this group. Additionally, SART data does not distinguish ectopic from heterotopic pregnancy. Previous studies have found the risk of heterotopic pregnancy lower than that of ectopic pregnancy: 0.1% in fresh autologous cycles and 0.06% in frozen autologous and donor cycles (1). Further elucidating this risk would help guide counseling for the risk of these distinct clinical entities, which differ in management options.

Furthermore, the investigators included cycles from 2004–2013. Practice pattern changes over the past decade are difficult to control for in the statistical analysis. Additionally, cycles were included only if they resulted in a pregnancy. While the risk of ectopic pregnancy in the setting of positive human chorionic gonadotropin (hCG) after embryo transfer is helpful, the overall risk of ectopic pregnancy from the cycle start would be helpful in patient counseling.

Despite these limitations, previous studies and human physiology support the notion that day 5 embryos are less likely to result in ectopic pregnancy than day 3 embryos. Aside from synchrony with the endometrium (implantation usually occurs at 5–7 days postfertilization), blastocyst transfer also provides protection from uterine contractility in the early luteal phase. Myometrial contractions from the cervix toward the fundus gradually decrease in frequency after ovulation, reaching a nearly quiescent stage 7 days after the hCG trigger (5). Additionally, blastocysts have a larger diameter than cleavage-stage embryos, so they may be more resistant to the contractile force of the myometrium (2).

It is always important to ask how studies such as this should change our current clinical practice. While the investigators statistically controlled for the number of embryos transferred, we need to continue advocating for single embryo transfers when appropriate. This is not only to minimize multiple pregnancy rates but also to minimize ectopic and heterotopic rates. Ectopic pregnancy rates increase with each additional embryo transferred: 1.6% with the transfer of one embryo vs. 1.7%, 2.2%, and 2.5% when two, three, or four or more embryos are transferred (1). We are also favoring blastocyst-stage transfer, but most providers who recommend cleavage-stage transfer today are doing so due to concern about culturing embryos to blastocyst resulting in a lower chance of pregnancy. This concern may arise from few two-pronuclear zygotes in an in vitro fertilization cycle or a history of poor blastocyst conversion in a prior cycle. While it is important to counsel on the risk of ectopic pregnancy, we would not recommend a day 5 over a day 3 transfer for these patients simply due to a 0.3% increased incidence of ectopic pregnancy. The statistically significant increased risk is not clinically significant by comparison.

Instead, we recommend that providers follow these pregnancies closely with serial hCG measurements and early ultrasound imaging if an abnormal hCG trend suggests increased ectopic risk.

Despite these limitations, this is the first analysis of a multicenter retrospective cohort comparing ectopic risk for day 3 vs. day 5 embryo transfers. Future studies assessing the heterotopic pregnancy risk while controlling for the number of embryos transferred and patient factors for tubal disease are needed to definitively promote a change in practice.

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REFERENCES

1. Perkins KM, Boulet SL, Kissin DM, Jamieson DJ. Risk of ectopic pregnancy associated with assisted reproductive technology in the United States, 2001-2011. Obstet Gynecol 2015;125:70–8.
2. Zhang B, Cui L, Tang R, Ding L, Yan L, Chen ZJ. Reduced ectopic pregnancy rate on day 5 embryo transfer compared with day 3: a meta-analysis. PLoS One 2017;12:169837.
3. Krishnamoorthy K, Greenberg P, Perlman B, Morelli S, Jindal S, McGovern P. The incidence of ectopic/heterotopic pregnancies after blastocyst-stage frozen-thawed embryo transfers compared with cleavage-stage: a SART CORS study. FS Rep 2021;2:421–427.
4. Shao R, Feng Y, Zou S, Weijdegård B, Wu G, Brännström M, et al. The role of estrogen in the pathophysiology of tubal ectopic pregnancy. Am J Transl Res 2012;4:269–78.
5. Fanchin R, Ayoubi JM, Righini C, Olivennes F, Schönauer LM, Frydman R. Uterine contractility decreases at the time of blastocyst transfers. Hum Reprod 2001;16:1115–9.