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REVIEW

# Ectopic pregnancy rates in frozen versus fresh embryo transfer in in vitro fertilization: A systematic review and meta-analysis



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## KEYWORDS

Ectopic;  
Fresh;  
Frozen;  
Embryo;  
Meta-analysis

**Abstract Objective:** To evaluate whether the rate of ectopic pregnancy differs between fresh and frozen embryo transfers.

*Design:* Systematic review and meta-analysis.

*Setting:* Centers for reproductive care.

*Materials and methods:* An electronic literature search in MEDLINE through PubMed was performed through December 2013. We included clinical trials comparing outcomes of in vitro fertilization (IVF) cycles between fresh and frozen embryo transfers.

*Main outcome measures:* Ectopic pregnancy rates from fresh versus frozen IVF cycles.

*Results:* A meta-analysis revealed no significant difference between ectopic pregnancy rates in fresh versus frozen embryo transfer. Similarly, there was no difference between ectopic pregnancy rates in natural-cycle frozen embryo transfer versus programmed cycles.

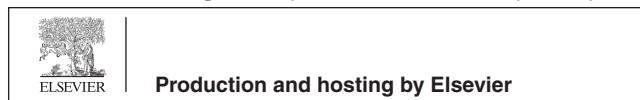
*Conclusions:* Differences in the hormonal milieu of the uterine environment between fresh and frozen embryo transfer stimulation do not appear to affect the ectopic pregnancy rate. More directed studies are needed before a definite recommendation can be made as to which is safer for prevention of ectopic pregnancy—fresh or frozen embryo transfer.

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## 1. Introduction

Ectopic pregnancy is an uncommon but serious complication of assisted reproductive technology (ART). The rate of ectopic pregnancy (EP), while less than 2% in the general population, ranges from 2 to 11% of pregnancies resulting from in vitro fertilization (IVF). While hypotheses for this discrepancy vary and may include issues inherent to the infertility populations studied (increased rates of tubal factor, etc), those studying this issue have suggested that the elevated rates of EP and other unfavorable IVF cycle outcomes may be caused in part by the supraphysiologic hormonal milieu resulting from autologous stimulation and can be traced to initial derangements in gene activation, angiogenesis and even placentation (1–5).

The topic of frozen embryo transfer (FET) has been a subject of recent debate in the IVF literature. Historically, FET has been used only in the event of failure to conceive with a fresh cycle or for future attempts to conceive. Thus, the “best quality” embryos were often used for the fresh transfer, followed by the lower-quality frozen–thawed embryos in subsequent cycles. New data, however, suggest that FET is at least as effective as fresh embryo transfer at achieving clinical pregnancy rates; a systematic review and meta-analysis by Roque et al. in 2013 showed similar clinical pregnancy rates, live birth rates, implantation rates, birth weights, and hemorrhage risks between IVF cycles with fresh and frozen transfer (6). FET is also known to decrease the incidence of ovarian hyperstimulation syndrome and so is often used with “super responders” or other patients at high risk of OHSS.

In contrast to fresh embryo transfer cycles where embryos are being transferred into highly stimulated endometrial environments, the hormonal milieu of an FET is much more similar to natural conception. This important distinction between fresh and frozen cycles results in very different uterine environments at the time of implantation and provides a unique opportunity to evaluate the effect of the supraphysiologic hormonal stimulation on EP rates following IVF cycles. Some researchers have proposed the idea that FET could afford similar pregnancy rates while allowing for recovery of the endometrium and adnexa, thereby increasing the receptivity of the endometrium and decreasing EP rates (7–14).

One meta-analysis comparing EP rates in fresh vs frozen embryo transfer was published in 2008 and showed similar outcomes between the two methods (15). However, multiple studies have been performed since that time, adding significantly to the available data for analysis. This meta-analysis

is intended to function as an update of the current literature concerning this subject, as well as to examine a subanalysis of natural versus programmed cycles for FET. Given the idea that it is the supraphysiologic hormonal levels achieved with ovarian stimulation that could confer a higher ectopic pregnancy rate with fresh cycles, we hypothesize that FET cycles in which the patient’s natural cycle is utilized (or supplemented with progesterone only) would have lower ectopic pregnancy rates than “programmed” cycles in which hormones are used to prepare the patient’s endometrium before embryo transfer. Additionally, several of the studies that we analyzed reported ectopic pregnancy rates in natural versus programmed frozen cycles, so we have included this data as a subanalysis in our study.

## 2. Methods

We included all studies (retrospective or prospective) reporting EP rates after fresh and frozen embryo transfers. We included all articles published up to the search date (without restricting by years), and we included all languages. We excluded national registry database reports/searches. This was done for two reasons: First, there was significant overlap between the large registry data and the data from individual studies. For example, in 2006 Clayton et al. published a study examining EP rates using data from the Society for Assisted Reproductive Technology (SART) (16). Because the vast majority of fertility centers in the US are members of SART, any publication citing single institution data between 1997 and 2001 were likely included his study. Therefore, our exclusion of large registry data prevented analysis of duplicate data. Furthermore, the exclusion of the national registry studies helped to prevent extreme skewing of the data due to much larger sample sizes in the national registry studies compared with the chart reviews from individual institutions. We also excluded any articles for which the outcome of ectopic pregnancy rate was not specifically referenced in figures or text. We excluded unpublished studies or abstracts. We excluded articles which mentioned ectopic pregnancy rates but did not report these rates for fresh versus frozen transfer, and we excluded articles which described ectopic pregnancy rates in day 3 versus day 5 fresh transfer but did not include frozen embryo transfer in the analysis.

We performed an Entrez/PubMed search of published data, using the search terms “embryo transfer” or “in vitro fertilization” and “ectopic pregnancy” on December 2, 2013. Two

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