# Ectopic pregnancy is not more likely following fresh vs frozen embryo transfer

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**Summary**

*Purpose:* To determine if the risk of ectopic pregnancy is greater following frozen vs fresh embryo transfer (ET).

*Methods:* Retrospective review of pregnancy outcome from January 1, 1997 to November 30, 2003. Cryopreservation was used as a simple freezing method and one-step removal of cryoprotectant. The cycles consisted mostly of graduated estradiol and progesterone supplementation.

*Results:* The ectopic pregnancy rate in 1,445 clinical pregnancies from fresh ET was 2.6% vs 2.0% of 975 clinical pregnancies resulting from frozen ET.

*Conclusion:* In contrast to the conclusions of two previous studies, the present study evaluating twice as many clinical pregnancies than the two aforementioned studies combined failed to show any greater risk of ectopic pregnancy when transfers were performed on day 3.

*Key words:* Frozen embryo; Ectopic pregnancy; Day 3 embryos.

## Introduction

Data was presented at the 2003 ASRM Meeting that frozen embryo transfer (ET) is twice as likely to result in ectopic pregnancy than fresh ET [1]. An evaluation of 3,000 clinical pregnancies at Bourn Hall Clinic found 135 ectopic pregnancies (4.5%) [2]. Pyrgiottis *et al.* evaluated 2,812 fresh ETs and found an overall 2.4% risk of ectopic pregnancies [3]. However they stated that the risk of ectopic pregnancies following frozen ET was higher (8/105, 7.6%) [3].

The objective of the present study was to corroborate or refute the aforementioned studies by evaluating a much larger number of pregnancies resulting from frozen ET.

## Materials and Methods

The outcome of all pregnancies resulting from in vitro fertilization (IVF) from January 1, 1997 to November 30, 2003 were evaluated in women up to age 49. This time period was chosen since from January 1, 1997 the transfer technique and transfer catheter was uniform, i.e., ultrasound guidance and Wallace catheter. Also there was a policy to remove hydrosalpinges prior to transfer. Donor oocyte transfers were included.

There were no exclusions even for decreased oocyte reserve as manifested by elevated day 3 serum FSH levels. Pregnancies resulting from blastocyst transfers were excluded. All transfers used 3-day-old embryos. Though some frozen ETs occurred in a natural cycle, the majority were with ovulation suppression by graduated dosages of estradiol followed by progesterone.

The embryos were cryopreserved using a simplified freezing protocol using a one-step removal of the cryoprotectant 1,2 propanediol with thawing [4].

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## Results

One thousand six hundred and thirty-four pregnancies resulting from fresh ET were compared to 1,144 pregnancies from frozen ET. There were 1,445 clinical pregnancies from fresh ET and 975 from frozen ETs. The clinical pregnancy rate (PRs) per transfer was 39.2% in the former and 36.1% in the latter (Table 1).

Thirty-eight of the 1,445 (2.6%) of the pregnancies resulting from fresh ET were ectopic. There were 20 ectopic pregnancies among the 975 (2.0%) frozen ETs ($p = 0.361$, NS) (Table 1).

## Conclusions

In contrast to the conclusions of the aforementioned studies, there was no evidence to suggest that the transfer of frozen-thawed embryos on day 3 leads to a greater chance of ectopic pregnancy compared to transfer of fresh embryos [1, 3]. The difference in conclusions may be related to the larger sample size of pregnancies from frozen ET in the present study.

One of the aforementioned studies suggested that transferring frozen/thawed blastocysts may reduce the risk of ectopic pregnancy from frozen ET but this does not explain the lower incidence found in the present study since they were only transferred on day 3 [1].

The study by Pyrgiottis *et al.* evaluated frozen ET in natural cycles [3]. Thus the possibility was that the higher risk of ectopic pregnancy following frozen ET might not be found in cycles using graduated estrogen followed by progesterone replacement. The study by Silva *et al.* also found a higher risk of ectopic pregnancies following frozen ET using estrogen supplementation [1].

Our data using mostly frozen ET cycles with estradiol/progesterone replacement found not even a trend toward a higher ectopic pregnancy rate with frozen ET.

Though our conclusions seem in the minority (since

Table 1. — *Rate of ectopic pregnancies resulting from fresh vs frozen embryo transfers.*

| | Fresh ET | Frozen ET |
|---|---|---|
| Clinical PR/transfer | 39.2% | 36.1% |
| Not pregnant | 1,445 | 975 |
| Number of ectopic pregnancies | 38 | 20 |
| % ectopic | 2.6% | 2.0% |

two other studies reached different conclusions), it should be noted that we evaluated twice as many frozen ET cycles as the other two studies combined. Thus with greater power the previously noted differences may disappear.

Another possible explanation for the disparity between the present study and the two other aforementioned ones is that we used a different freeze/thaw protocol. The possibility is that our protocol allows the embryos to have a greater chance of implanting into the endometrium.

The study by Silva *et al.* suggested that transferring at the blastocyst stage might possibly reduce the propensity for frozen embryos to implant in the fallopian tubes [1]. A study by Milki *et al.* failed to demonstrate any reduction in the ectopic pregnancy rate by allowing the frozen embryo to develop to the blastocyst stage before transferring [5].

Thus with our study showing no increase in ectopic pregnancy rates with transfer of day 3 frozen/thawed embryos vs day 3 fresh embryos and the data from Milki *et al.*, it does not seem reasonable to purposely allow a frozen embryo to develop to the blastocyst stage just to reduce the risk of ectopic pregnancy.

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