

Embryo transfer technique as a cause of ectopic pregnancy in in vitro fertilization*

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Part of the quality control for the Cooper Center for In Vitro Fertilization is to evaluate separately the pregnancy rates (PRs) per retrieval and per transfer according to physicians. One physician appeared to have the highest PR per transfer and after evaluating the techniques it was determined that this particular physician, in contrast with the others, did not use a midfundal transfer technique, but instead delivered the embryos < 5 mm from the fundus. Based on this retrospective analysis, a prospective study was designed to compare intrauterine pregnancy (IUP) rates and ectopic pregnancy (EP) rates after midfundal versus deep fundal ETs after IVF.

MATERIALS AND METHODS

Five physicians participated in this study. Two were designated to use a deep fundal transfer and the other three physicians used the midfundal technique (>15 mm from fundus). Four controlled ovarian hyperstimulation (COH) regimens were used for fresh ETs: luteal phase leuprolide acetate (LA)-gonadotropin regimen (90% of cycles), short flare technique, hMG only, and clomiphene citrate

(CC)-gonadotropins. The patients were assigned to the two groups randomly, regardless of their COH regimens. Therefore, both groups contained similar proportions of patients on different COH regimens.

Embryo Transfer Procedure

The short Frydman Embryo Transfer Set (CCD International, Natick, MA) was used for embryo replacement into the uterus. The set consists of a cannula with a removable metal stylet and an ET catheter with an inner steel tube in the upper part of the catheter. The cannula is inserted into the cervix and the stylet is removed.

In the IVF laboratory the catheter is attached to a 1-mL syringe and rinsed up to the metal rod with ET media. Embryo transfer media consists of HEPES-buffered human tubal fluid medium (no. 1092; Irvine Scientific, Irvine, CA). Air is introduced into the syringe up to the 0.05-mL mark. A 5- μ L column of transfer media is aspirated into the catheter followed by the same volume of air. The embryos are placed in an organ culture dish in 1 mL of transfer media and then loaded into the catheter in 5 μ L of transfer media. This column with embryos is followed by 5 μ L of air and a final column of 5 μ L of transfer media.

The embryologist hands the transfer catheter through a window in the IVF laboratory into the transfer room. The physician places the catheter into the uterus and expels the embryos and the

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extra 0.05 mL of air. The uterine depth from the external os had been previously determined during a mock transfer procedure. The distance from the fundus during the actual transfers was based on the external os-fundus depth measured during the mock transfer. The catheter is held in this position for 1 minute after the transfer to allow the embryos to fall away from the catheter. The catheter and cannula are removed from the uterus and handed back to the embryologist. The embryologist rinses the catheter and cannula with ET media to ensure that no embryos remained inside.

RESULTS

There were 1590 transfers evaluated (including fresh and frozen ETs). There were 200 (12.5%) clinical pregnancies (gestational sac seen intrauterine) and 14 EPs (7.0% of all pregnancies were EPs). The deep fundal technique was used in 660 ETs and the midfundal was used in 930 ETs. There were 82 pregnancies using deep fundal technique (12.4%) and 132 pregnancies (14.2%) for the midfundal transfer group. Ten EPs occurred in 660 (1.5%) deep fundal transfers and 4 in 930 (0.4%) midfundal transfers. Thus, 10 of 82 (12.2%) pregnancies after deep fundal transfer resulted in EPs compared with only 4 of 132 (3%) with the midfundal technique. The difference in the rate of EPs with the two techniques of transfer was significant (Fisher's Exact Test, $P = 0.029$).

Tubal disease was noted in 49% versus 46.5% of those receiving deep versus midcavity transfer, respectively. All EPs occurred in women with tubal pathology.

The number and percentage of EPs according to COH regimen used (irrespective of midfundal or deep fundal transfer technique) were as follows: luteal phase LA, 11 EPs (7%); hMG, 2 (3%); and flare technique, 1 (3.2%). Considering the very low number of the ectopics with hMG and flare techniques and low proportion of transfers performed with these techniques, the difference probably could not be considered significant.

DISCUSSION

The relationship of the transfer techniques in ET to the success and complications of IVF has been a subject of interest and discussion since the introduction of this technology.

Yovich et al. (1) evaluated the same two transfer

techniques that we evaluated in this study and found 4 of 24 pregnancies were ectopic (25%) with deep fundal transfers versus only 1 EP in 56 (1.7%) using midfundal transfer (1). Interestingly, 2 of the 14 pregnancies in the study presented herein were heterotopic pregnancies. Dimitry et al. (2) reported heterotopic pregnancies in 9 of 312 IVF (2.9%) pregnancies despite the fact that heterotopic pregnancy has been estimated to be as infrequent as 1:30,000 (3). The 4.2% rate of EPs in midfundal transfer in this study is consistent with the 4.0% risk of EPs reported by Cohen et al. (4) in 1,163 IVF pregnancies.

Five physicians participated in this study. Ideally the study would have been less biased if only a single physician would have done both types of transfers during the whole study. This would have precluded an adequate sample size in a reasonable length of time. However, to overcome this possible difficulty, we evaluated the results of the transfers by the two physicians who were performing the deep transfers, because they changed to the midcavity technique at the termination of the reported study. Of 285 ETs performed by the midcavity method, they had 70 pregnancies (PR = 24.5% per ET) and two cases of EP (2.8%). This confirms the increased risk of the deep fundal transfer in leading to EPs. Because no higher intrauterine pregnancy rate was found with the deep method, the midcavity approach is the preferred technique. The explanation behind the higher ectopic rate in the deep fundal method might be the closer proximity of the embryos to the tubes and that the fundal contact might exacerbate the uterine activity, which could force the embryos in a retrograde direction.

SUMMARY

A randomized prospective study was performed to compare the effects of a midfundal versus a deep fundal transfer technique on subsequent intrauterine and ectopic PRs after IVF. The clinical intrauterine PR after the deep fundal transfer was 12.4% per cycle with a 1.5% ectopic PR (which represented 12.2% of the pregnancies) versus 14.2% IUPs per cycle with a 0.4% ectopic rate (representing 3% of pregnancies) after midfundal transfers. The midfundal technique appears superior to deep fundal procedures because of a lower percentage of EPs without any sacrifice of the intrauterine PR after midfundal transfers.

Key Words: Midfundal, deep fundal, embryo transfer, ectopic, heterotopic

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