

## Embryo transfer technique as a cause of ectopic pregnancies in in vitro fertilization\*

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*Against an overall risk of around 2% ectopic pregnancies in in vitro fertilization programs around the world, we report an incidence more than three times greater (5 tubal ectopic pregnancies in 80 clinical in vitro fertilization pregnancies). Of two techniques used for embryo transfers, one produced a significantly higher risk for ectopic pregnancy ( $P < 0.05$ ). Four of the ectopic pregnancies occurred in a small group of 24 patients in whom the embryo transfer technique attempted to deliver the embryos at the uterine fundus (mean distance of catheter insertion  $62.9 \pm 7.9$  mm from the external cervical os). Only one ectopic pregnancy occurred in 56 patients whose embryos were transferred to a standard, generally midcavity position. It is concluded that the delivery catheter need be inserted only 55 mm as a routine and less in patients with a shortened cervix or with the hypoplastic uterus usually encountered in women with primary ovarian failure who have ovum or embryo donation. In such cases an ultrasonic measurement of length may indicate that a shorter transfer distance is required. *Fertil Steril* 44:318, 1985*

The very first reported human pregnancy after in vitro fertilization and embryo transfer (IVF-ET) was an ectopic pregnancy.<sup>1</sup> The phenomenon led to the recommendation that the diseased fallopian tubes should be removed or ligated before a patient's inclusion in an IVF program.<sup>2</sup> However, there has been a general reluctance to carry out the recommendation, especially because many IVF-ET pregnancies are now generated in pa-

tients whose underlying cause of infertility is nontubal. Ectopic pregnancies continue to be reported from a number of centers, and the collaborative results presented at the III World Congress of IVF-ET in Helsinki documented 19 tubal ectopic pregnancies from 1084 clinically detected pregnancies (1.8%), of which 572 were ongoing (ectopic rate, 3.3%).<sup>3</sup> We report a higher tubal ectopic pregnancy rate, and the condition is analyzed with respect to ET techniques.

### MATERIALS AND METHODS

During the years 1981 to 1984, the IVF-ET program in which PIVET Laboratory and the University of Western Australia have collaborated has generated 80 clinically detected pregnancies from an overall series of 650 laparoscopic aspirations. The techniques have been fully described.<sup>4</sup>

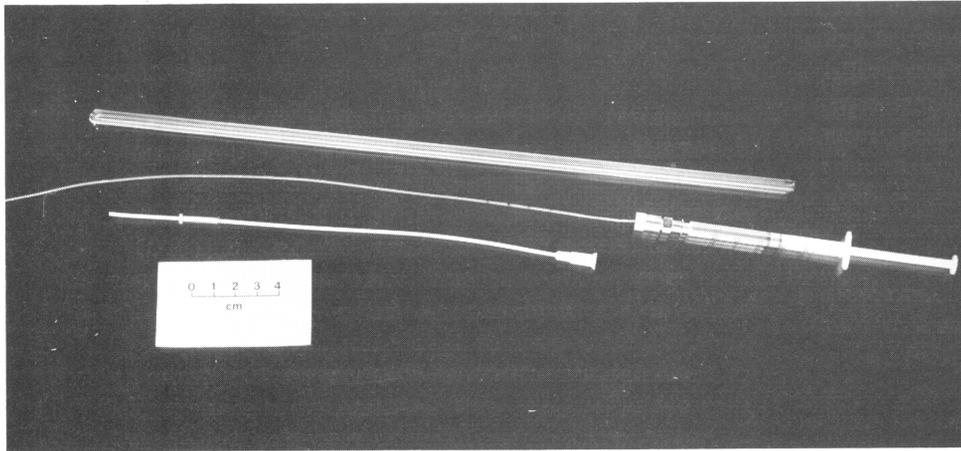
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Received February 4, 1985; revised and accepted May 17, 1985.

\*Supported by the University of Western Australia grant 4LIRBZQ1083/84.

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**Figure 1**  
Tuberculin syringe attached to the ET catheter, which has 1-cm markings beginning at the length of the external catheter, which is designed to be inserted 4 cm into the cervical canal. The upper glass tube is the storage container for the ET catheter.

All ETs were undertaken with the patients in the Trendelenburg position with a 20° head-down tilt. The ET delivery system is depicted in Figure 1. A double-catheter technique was used. The outer catheter had an internal diameter of 1.40 mm and an external diameter of 1.70 mm. Initially, it was composed of polyurethane, but over the past 2 years a Vialon polymer resin catheter was used (Deseret Medical Inc., Sandy, UT). An inner catheter conveyed the embryos. It was composed of Teflon (William Cook Pty. Ltd., Melbourne, Victoria, Australia), with an internal diameter of 0.74 mm, outer diameter of 1.33 mm, and length of 30 cm. Both catheter materials were shown to be nontoxic to mouse embryos, allowing > 80% (similar to a control group) to develop from 2-cell to the expanded blastocyst stage when cultured in the presence of catheter segments. The uterine end of the Teflon catheter had a bullet-nose shape and an end hole. The external end had a stainless steel Luer-lock fitting to which was attached a standard tuberculin syringe (Terumo [Australia] Pty. Ltd., Melbourne, Victoria, Australia) containing culture medium.

At the time of ET, the Vialon catheter was removed from its wrappings and a silicon marker was placed exactly 4.0 cm from its tip. The patient was then placed in the lithotomy position with a 20° head-down tilt, and a bivalve speculum illuminated from a cold light source was inserted into the vagina to expose the cervix. Mucus was gently wiped from the cervix with a dry swab, and then the external os was moistened with a small dab soaked in culture medium. The Vialon catheter was gently and slowly manipulated through the cervical canal with a long forceps with a right-angled tip until the silicon rubber marker abut-

ted against the external cervical os. More than 90% of transfers required no tenaculum on the cervix; we simply manipulated the speculum to induce a straightened uterocervical canal. Occasionally a tenaculum was applied to the anterior cervical lip (well away from the cervical os). The tenaculum could be applied slowly without causing discomfort, and then by gentle traction the cervical canal was straightened. Rarely was a 4-mm cervical dilator required for identification of the canal, and on only two occasions did the transfer procedure prove to be too difficult, requiring a repeat procedure under general anesthesia the following day.

Once the external catheter was in position, the Teflon tube was filled with culture medium from the tuberculin syringe. The embryos were now moved from the culture site in the incubator across to the stereomicroscope. A small air space was created at the tip of the Teflon catheter, and between one and four embryos were loaded into a 30- $\mu$ l segment of culture medium. Again a small air space was created at the tip so that the transfer segment was discretely placed in the final 3 cm of the transfer catheter, which was now threaded down the outer catheter, with the application of method A or B. Once the inner catheter was positioned, the outer catheter was withdrawn back to the Luer hub and, after a settling period of 60 seconds, the embryos were transferred out of the inner catheter by the injection of the tuberculin syringe precisely five fine segments (50  $\mu$ l). The catheter was then immediately slowly withdrawn.

Three gynecologists undertook the ETs in this program, two using the technique known as method A and one using the technique known as

method B. Method A involved insertion of the inner catheter precisely 1.5 cm from the tip of the outer catheter. The distance was measured from 1-cm markings on the inner catheter placed so that the first marking was noted at the Luer hub of the outer catheter when the inner one precisely reached the tip of the outer catheter. All catheters were checked for accuracy of marking before inclusion in the ET set. With method A, the embryos were always transferred at a set distance of 55 mm or less from the external cervical os (occasionally the uterine length was only 50 mm, noted in women with a surgically shortened cervix or in those with primary ovarian failure who had ovum or embryo donation and who had a hypoplastic uterus). Method B involved threading the inner catheter gently into the uterine cavity until it could not progress further. When the catheter tip touched what was presumed to be the uterine fundus and slight kinking was recognized, it was withdrawn 3 or 4 mm before ET. The measurements recorded with this technique showed that the inner catheter was threaded to distances between 55 and 90 mm (mean  $\pm$  standard deviation, 62.9  $\pm$  7.9 mm) from the external os. Ultrasonic (Diasonics Digital Radio Frequency 1, Diasonics Pty. Ltd., Milpitas, CA) measurements of uterine length were also recorded for each case. Most uterocervical canals measured between 55 and 63 mm on ultrasound (mean  $\pm$  standard deviation, 59.3  $\pm$  4.2 mm), and the maximum length reported was 68 mm, including cases where the internal catheter was introduced up to 90 mm within the uterus.

## RESULTS

The two techniques of ET gave rise to similar pregnancy rates (Table 1). During this series five tubal ectopic pregnancies occurred, necessitating either partial or complete salpingectomy. It was of interest that one of the tubal ectopic pregnancies occurred in combination with an intrauterine pregnancy. Trophoblastic tissue was identified in the excised tubal lumen of each case at histologic examination. The observation of a higher ectopic rate with method B does reach the level of statistical significance ( $\chi^2 = 4.06$ , 1 degree of freedom [*df*];  $P < 0.05$ ). The catheter insertion distance for that group was significantly higher than for method A ( $t = 4.90$ , 23 *df*;  $P < 0.001$ ). Also, all the ectopic pregnancies with method B occurred when the inner catheter was inserted  $> 60$  mm from the

Table 1. Pregnancy and Ectopic Rate Related to Method of ET

Technique	No. of embryo transfers	Pregnancies	% of ET	No. of ectopics
Method A	406	56	14	1
Method B	190	24	13 <sup>a</sup>	4 <sup>b</sup>

<sup>a</sup>Includes one heterotopic pregnancy.

<sup>b</sup>Chi-square = 4.06, 1 *df*;  $P < 0.05$ .

external os. Each was described as an easy transfer, and no unusual features of patient management were recognized.

Three of the ectopic pregnancies occurred in women who had diagnosed tubal disease, whereas two of the patients, both of whom were undergoing IVF because of oligospermia, were considered to have normal fallopian tubes.

## DISCUSSION

Five ectopic pregnancies arising from a series of 80 clinically detected pregnancies is at least three times higher than the overall rate for IVF-ET. In one series, 4 ectopic pregnancies in 24 pregnancies (16%) is inordinately high; the data imply that this was related to the use of high insertion of the transfer catheter in order for the catheter to touch the uterine fundus. The insertion distance was always greater in method B, and on several occasions the catheter was introduced deeper than suggested possible by the preliminary ultrasound measurement. In those cases it was likely that the catheter was diverted to the cornual regions of the uterus, which brought it into proximity with the uterotubal junction and possibly into the tubal orifice on some occasions. Because most of the ectopic pregnancies occurred when the catheter was inserted  $> 60$  mm, this method was prone to cause at least some of the embryos to enter or be placed in the tubal lumen. Other aspects of the ET technique, such as lithotomy and head-down tilt positions, prolonged head-down tilt after transfer, and the transfer of embryos in 50% maternal serum, are unlikely to be relevant because such techniques were applied equally for patients transferred by methods A and B.

Natural conception is known to occur in the fallopian tube, and the embryos enter the uterine cavity approximately 4 days after fertilization. It may be expected that embryos inserted into the fallopian tube 2 days after fertilization in the IVF program should be returned to the uterus by the natural mechanism of tubal and ciliary motility.

Women undergoing IVF because of known tubal disease may develop ectopic pregnancies because of failure of the tubal transport mechanisms, but it is of interest that two of the cases in this series had no known tubal disease. However, tubal motility may be abnormal in hyperstimulated cycles because there is a high ectopic and heterotopic pregnancy rate in women treated with gonadotropin injections.<sup>5, 6</sup>

Various transcervical ET techniques have been described involving single- and double-catheter systems, different positions of the patient depending on anteversion or retroversion of the uterus, and attention to the embryo expulsion site in relationship to the inner uterine fundus. In the series described in this article, all patients were transferred in the same position, only the double-catheter system was used, and the only variation applicable to the two groups was the site of embryo expulsion. It would appear that the fixed-length transfer site (55 mm from the external os) achieves a pregnancy rate equal to that of the transfer catheter touching the uterine fundus and being withdrawn a few millimeters before transfer. However, the former technique is associated with a reduced risk of ectopic pregnancy and is now the preferred technique in this program. A hypothesis has previously been proposed that the risk of ectopic pregnancies may be minimized by transfer of the embryos in < 50  $\mu$ l of culture fluid and placement in the midcavity rather than near the fundus.<sup>7</sup> Our data prove the relevance of ET position but indicate that as far as ET volume is concerned, ectopic pregnancies will still occur when the embryos are conveyed in < 50  $\mu$ l of culture fluid. The value of ultrasonic measure-

ment of uterine length is limited in the fixed length ET method, because few cases have uterine lengths < 55 mm. Its use could be reserved for those patients with surgically shortened cervixes or patients with primary ovarian failure having ovum or embryo donation because they tend to have a smaller, hypoplastic uterus.

*Acknowledgments.* We thank Peter Braidahl, F.R.A.C.R., Michael Gibson, F.R.A.C.R., and Bill Thomas, D.M.U., for all ultrasound investigations.

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