

Heterotopic Pregnancy from in Vitro Fertilization

JOHN L. YOVICH,^{1,2} SUSAN C. McCOLM,¹ SIMON R. TURNER,³ and PHILLIP L. MATSON³

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A case of heterotopic or combined intrauterine and tubal ectopic pregnancy is described following in vitro fertilization and the transfer of five four-cell embryos. The phenomenon is known to be related to ovarian stimulation by gonadotropin therapy, and there is an increased risk with underlying tubal disease. This patient had both variables. Techniques applied at the time of embryo transfer are also implicated, namely, the use of culture medium with 50% maternal serum to convey the embryos to the uterus, the catheterization method, and the position of the patient during transfer.

KEY WORDS: ectopic pregnancy; combined (heterotopic) pregnancy; embryo transfer; in vitro fertilization.

INTRODUCTION

Previously we have reported on the increasing incidence of heterotopic or combined pregnancies seen in women managed for infertility, especially when treated with gonadotropin therapy to induce ovulation (1). The phenomenon is related to the risk of ectopic pregnancy and the incidence of multiple ovulations. The incidence of multiple pregnancy in a series of 108 pregnancies arising following gonadotropin therapy (both human menopausal gonadotropin and human pituitary gonadotropin) in our experience is 26% (2). Given an increased risk of ectopic pregnancy of more than 1 in 80 of our local population, the risk of heterotopic pregnancies among infertile women treated with gonadotropins is therefore of the order of 1 in 300. The following

case report is the fourth heterotopic pregnancy diagnosed in this clinic during the years 1980–1984, among approximately 700 pregnancies generated from various infertility treatments including 108 in vitro fertilization (IVF) pregnancies.

MATERIALS AND METHODS

Case History

The patient is a 34-year-old married Caucasian female who conceived in her second treatment by in vitro fertilization and embryo transfer (IVF-ET). The history was of 8 years of infertility due to pelvic inflammatory disease. Following an initial diagnosis of bilateral hydrosalpinges and a posterior cervical leiomyoma, three separate reconstructive tubal operations were performed, which included salpingolysis and salpingostomy on each occasion and myomectomy during the third operation. However, pregnancy failed to ensue and a review laparoscopy revealed a right hydrosalpinx and fimbrial agglutination of the left fallopian tube with markedly impeded flow of dye on perturbation.

At the first IVF-ET treatment cycle, follicular development was stimulated with clomiphene citrate (Clomid, Merrell Dow, Cincinnati, Ohio), 150 mg on days 2 to 6, with human chorionic gonadotropin (hCG), 5000 U, given on day 12. Four mature oocytes were aspirated 36 hr later, and three embryos were transferred 44 hr postinsemination (1 × two cell, 2 × four cell). The techniques have been fully described previously (3).

Unfortunately pregnancy failed to ensue, and 8 months later IVF was again undertaken. On this occasion follicular development was stimulated with a combination of clomiphene citrate (100 mg, days 2 to 6) and human menopausal gonadotropins

¹ University Department of Obstetrics and Gynaecology, King Edward Memorial Hospital, Bagot Road, Subiaco, Western Australia 6008.

² To whom correspondence should be addressed at Pivet Medical Centre, 166-168 Cambridge Street, Leederville, Perth, Western Australia.

³ PIVET Laboratory, Cambridge Hospital, Wembley, Perth, Western Australia 6014.

[hMG; Humegon, Organon (Australia) Pty. Ltd., NSW, Australia], 2 ampoules/day on days 4–8 and 3 ampoules on days 9–11. Oocyte recovery was undertaken 36 hr after an injection of hCG given when the level of serum estradiol-17 β (E₂) was 7025 pmol/liter, serum progesterone was 2.0 nmol/liter, and serum luteinizing hormone was 6.4 IU/liter. The cervical mucus score had risen, and ultrasound demonstrated eight ovarian follicles \geq 1.6 cm. The E₂ level was 9045 pmol/liter the next morning, and at laparoscopy a mature oocyte was recovered from the eight large follicles, and an additional three oocytes from smaller follicles in the range of 1.0 to 1.2 cm. Nine oocytes fertilized successfully and all were four-cell embryos 44 hr postinsemination when embryo transfer was carried out. Five embryos were transferred and four were stored by cryopreservation.

The embryo transfer technique has been described previously (3). Briefly, a double-catheter technique is used. The outer catheter, now composed of vialon, traverses the cervix for a set measurement of 4 cm. An inner catheter composed of Teflon, containing the embryos held in 30 μ l of culture medium with 50% deactivated maternal serum, is inserted through the outer catheter to a set distance of 5.5 cm from the external os. The outer catheter is then withdrawn, and following a waiting period of 60 sec, the 30- μ l segment containing the embryos is injected slowly into the uterine cavity. For the procedure, the patient was placed in the lithotomy position with a 20° head-down tilt. After transfer, she returned to her bed, with the head-down tilt maintained for 6 hr. Thereafter, the bed was leveled and the patient discharged home the following morning.

On day 16 of the luteal phase, pregnancy was confirmed with serum levels of E₂ at 9020 pmol/liter, progesterone at 630 nmol/liter, and β -hCG at 220 IU/liter. Thereafter weekly quantitative β -hCG assays confirmed rising levels in accordance with an ongoing pregnancy. Five weeks after embryo transfer ultrasound revealed two intrauterine gestational sacs, one of which contained fetal parts and fetal heart movement. The second sac was smaller and considered to be a possible blighted ovum (Fig. 1). Both ovaries were noted to contain several cystic areas, up to 5 cm in diameter, consistent with the follicular stimulation regime. Figure 2 summarizes the patient's clinical course. Prior to the ultrasound investigation, she developed uterine bleeding and persistent left pelvic pain of a boring



Fig. 1. Longitudinal scan of uterus displaying two gestational sacs within the uterus. The upper sac (left) contains fetal parts and heart movement was detected. The lower sac (right) is smaller and irregular and no fetal parts were identified, suggesting a blighted ovum.

nature. Her symptoms persisted over the ensuing 7 days, despite total bed rest in hospital and intramuscular analgesia. The differential diagnosis was considered to be a ruptured ovarian cyst or a coexistent ectopic pregnancy. Laparoscopy was undertaken at 8 weeks of gestation (dated from the last menstrual period) and this confirmed a left midtubal swelling consistent with ectopic pregnancy. Both ovaries were noted to be multicystic without any evidence of rupture. The uterus was evenly enlarged, consistent with intrauterine pregnancy. A small amount of dark blood was issuing from the distal left fallopian tube, and there was approximately 200 ml in the pelvic cavity. Laparotomy was proceeded with forthwith, and the left fallopian tube exised (Fig. 3). The right fallopian tube was noted to have a distal occlusion but was left intact. Subsequent histology confirmed an ectopic pregnancy and revealed the wall of the excised tube to be extremely thin and the lumen filled with blood clot in which numerous degenerate immature chorionic villi were present. An acute inflammatory reaction was noted adjacent to the implantation site.

Over the ensuing week, the patient made an uneventful recovery, and the uterine bleeding gradually resolved. At the ninth week of gestation, the serum profile revealed a quantitative β -hCG level at 57,000 IU/liter, serum progesterone at 335 nmol/liter, and E₂ at 7890 pmol/liter. An ultrasound scan was repeated during the 12th week after menses.

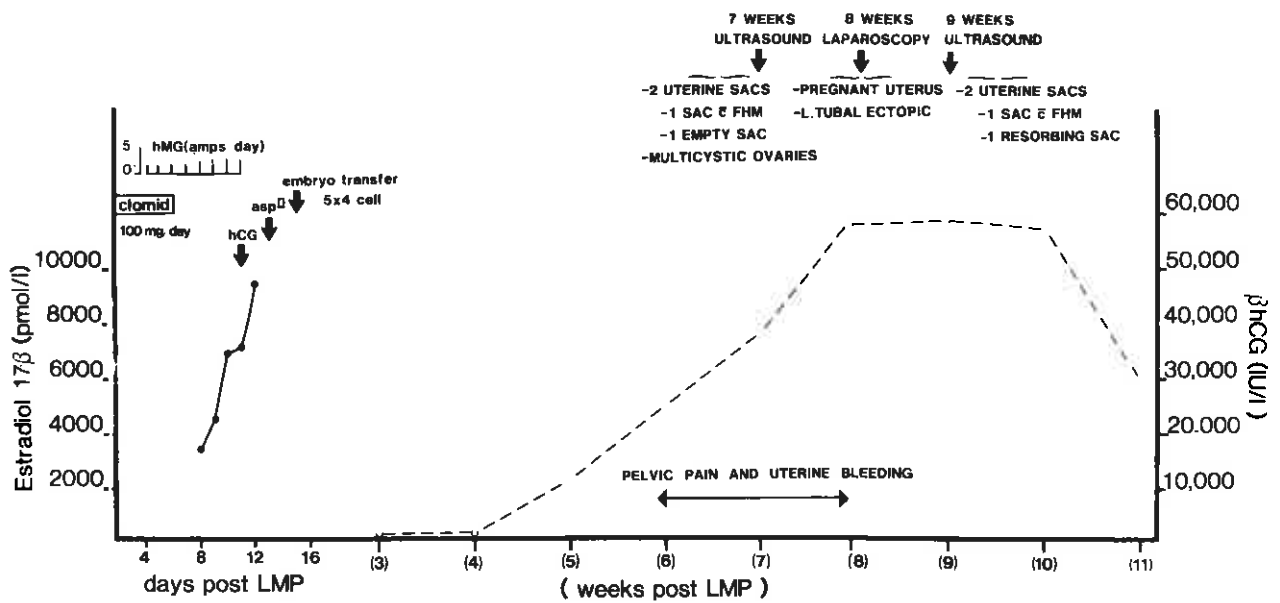


Fig. 2. Depicts the clinical course of the patient who developed a heterotopic pregnancy after the transfer of five embryos into the uterus, set against the hormonal response in the follicular phase and the β -hCG profile during the first trimester of pregnancy.

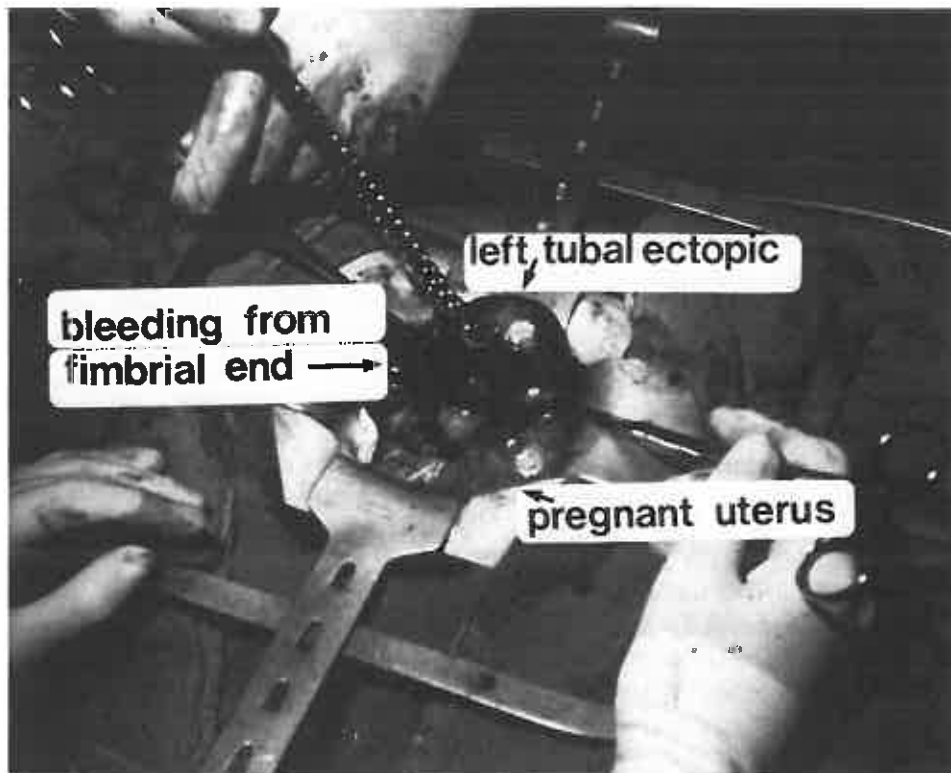


Fig. 3. Laparotomy findings of the patient who had persistent pelvic pain and uterine bleeding. The left fallopian tube contained an ectopic pregnancy (histologically confirmed) in the ampullary-isthmic region, with active bleeding via the fimbrial end. The uterus was enlarged, consistent with the ultrasound finding of two intrauterine pregnancy sacs.

Only one sac was then detected in the uterus. It contained a single fetus with both heart and limb movement. The crown-rump length was 49 mm and the biparietal diameter 19 mm, consistent with the gestational dates. At this stage neither ovary contained cysts. A further clinical and sequential ultrasound assessment indicates a pregnancy developing normally, currently at 30 weeks of gestation.

DISCUSSION

Of 1084 clinically detected pregnancies arising from IVF-ET therapy, 19 ectopic pregnancies were reported at the Third World Congress on IVF-ET held in Helsinki (4). The cause of ectopic pregnancies in IVF remains unknown but is probably related to the embryo transfer technique (5). This case report documents the first heterotopic pregnancy from IVF-ET.

Combined or heterotopic pregnancies are a well-described risk for patients undergoing ovulation induction with gonadotropins (1). The risk is related to the level of estrogen excretion as measured in the urine and the rate of rise of estrogen output during the coasting phase between the last injection of human menopausal or pituitary gonadotropin and the trigger injection of hCG for follicle dispersal (2.3- to 3.2-fold rise). The risk of noncombined ectopic pregnancies is also increased after gonadotropin therapy (6), and again it has been related to the level of urinary estrogens excreted. In the patient reported here, the hCG injection was given 14 hr after the previous hMG injection, and we did not record the urinary estrogen output. However, the serum E_2 level was documented the following morning, and the rise over the entire 24-hr period was 34%.

We have documented 4 noncombined ectopic pregnancies in an IVF series of 80 clinical pregnancies. Most, but not all, cases ensued in patients with known tubal disease, the cause in IVF being more related to the length of insertion of the inner catheter, giving rise to the possibility that embryos were in fact inserted at the uterotubal orifice or possibly in the tubal lumen itself (5). However, in this case report, two of the five embryos implanted in the uterus and one in the fallopian tube, and so it is more likely that one of the embryos "migrated" into the tube. This may have been assisted by the head-down tilt position to allow the embryo to

move under the force of gravity. Also, the influence of the heavy medium (50% maternal serum added) should not be excluded since transfers in 75–90% serum result in a higher pregnancy rate than those in 15–20% serum (7). This was attributed to a reduced leakage of fluid back along the outside of the catheter into the cervical canal, and so possibly the heavier medium helps the delivery of the embryos to the fundus. The volume of medium transferred (30 μ l) is not extreme and the role seems minimal, especially since overall pregnancy rates are not influenced by the volume transferred over the range 20 to 50 μ l (7).

Whatever the cause of heterotopic pregnancy in this case of IVF-ET, the possibility must be kept in mind in those patients who have had several embryos transferred and who develop a combination of uterine bleeding and pelvic pain. The finding of an intrauterine gestation on ultrasound does not preclude the possibility of a coexisting ectopic pregnancy in the fallopian tube, and as we have previously documented (1), the condition can lead to maternal collapse from intrapelvic hemorrhage which is potentially lethal. The early recourse to laparoscopy in such cases provides an effective means of diagnosis and early treatment, with a high chance of successful outcome for the intrauterine pregnancy.

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NOTE ADDED IN PROOF

A healthy male infant weighing 3250 grams was delivered by elective caesarian section on March 6, 1985.

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