

Risk Factors for Ectopic Pregnancy After *in Vitro* Fertilization and Embryo Transfer¹

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Purpose: To find the incidence of ectopic pregnancy (EP) in patients who conceived in the IVF-ET program, and risk factors affecting the occurrence of EP.

Methods: We analyzed the effects of the indication for IVF, type of ovarian stimulation (hMG + hCG vs. GnRH + hMG + hCG), type of embryo transfer (transcervical intratubal, intrauterine in chest-knee position and intrauterine in lithotomy position) and number of embryos transferred on the occurrence of EP. EP was treated by laparotomy, prostaglandin E₂ or laparoscopic surgery.

Results: In 7991 stimulated and 92 natural cycles treated in the Ljubljana IVF-ET program between May 1983 and June 1994 we achieved 1059 pregnancies, of which 44 were ectopic (incidence 4.1%), the main risk being tubal factor infertility. There were 38 (86.3%) tubal, 3 (6.8%) heterotopic, 1 (2.4%) ovarian, and 2 (4.5%) cornual EP. In two patients multiple tubal EP occurred (1 twin, 1 triplet). Forty-two patients (95.4%) had tubal factor infertility, 1 (2.3%) unexplained, and 1 (2.3%) patient had male factor. The incidence of EP in patients with tubal infertility was 5.4%, in patients with unexplained infertility 2.0% and in those with male factor 0.9%. There appeared to be no correlation between the two superovulatory methods. With transcervical intrauterine ET the incidence of EP was 0 of 5 clinical pregnancies (CP); with intrauterine in chest-knee position it was 26 (3.5%) of 738 CP; with intrauterine in lithotomy position it was 17 (5.4%) of 316 CP. The difference between the two types of intrauterine ET is not statistically significant. The incidence of EP did not correlate with the number of embryos transferred. The average initial values of beta hCG per-

formed 17 days after ET were significantly lower in patients with EP than in those with normal singleton pregnancy (157 ± 143 mIU/ml vs. 408 ± 148 mIU/ml).

Conclusions: EP can complicate the IVF procedure. The main risk factor is tubal infertility with or without previous tubal surgery. The low initial value of beta hCG has a strong predictive value in the diagnosis of EP.

KEY WORDS: IVF-ET; ectopic pregnancy.

INTRODUCTION

The very first pregnancy achieved in an *in vitro* fertilization (IVF) was ectopic (EP) (1). With the development of the procedure and its wide use in infertility treatment EP has become one of the constant complications of the procedure with the incidence ranging from 2% to 11% (2–4). Besides singleton tubal EP, its rarer types, such as multiple tubal and heterotopic tubal EP occur more frequently after the IVF-ET procedure (5). Most frequently encountered factors involved in the occurrence of EP are tubal factors of infertility (6), ovulation stimulation (7,8), type of embryo transfer (ET) (2) and volume of culture medium at ET (9). In the retrospective study we analyzed risk factors in 44 EP in the Ljubljana IVF-ET program from May 1983 to June 1994, principally with regard to the indication for IVF-ET, type of ovarian stimulation, type of ET and number of embryos transferred.

MATERIALS AND METHODS

In the period 1 May 1983–30 June 1994 IVF-ET was undergone by 3226 women in 7991 stimulated and in 92 natural cycles. The most common indication of IVF-ET was tubal factor infertility (1531 cycles). Follow the male factor (1121 cycles), endo-

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metriosis (367 cycles), unexplained infertility (283 cycles) and other factors (369 cycles).

For ovarian stimulation we used various protocol regimens. Clomiphene citrate (CC) (Klomifen, Belupo, Croatia), human menopausal gonadotropin (hMG) (Pergonal, Metrodin, Serono, Italy) and human chorionic gonadotropin (hCG) (Primogonyl, Schering, Germany) was used in 239 cycles, hMG and hCG in 5996 cycles, gonadotropin releasing hormone analogues (GnRH-a) (Suprefact, Hoechst AG, Germany; Decapeptyl, Ipsen-Biotech, Paris, France), hMG and hCG in 1532 cycles. In 63 patients with poor ovarian responsiveness we added growth hormone (GH) (Novotropin, Novo Nordisk, Denmark).

Until 1987 oocytes were retrieved laparoscopically under general anesthesia (10) and thereafter with transvaginal ultrasound-guided follicular aspiration under local anesthesia (11).

For laboratory procedure we used the technique as described by Lopata (12). For fertilization only husband's semen was used, also in cases of insufficient semen quality. We performed 5624 ET, 5588 into the uterus using Frydman's bichannel catheter, and 36 transcervical intratubal ET using the catheter according to Jansen and Anderson (13). Embryos were transferred in 10–40 μ l of the culture medium 0.5 cm below the uterine fundus. Until 1992 we performed ET in chest-knee position in women with anteverted uterus, and in lithotomy position in women with retroverted uterus. Since 1992 ET has been performed in lithotomy position regardless of the position of the uterus. Until 1991 the highest number of transferred embryos was 6, and has been 4 since.

Of 44 EP there were 38 (86.3%) tubal, 3 (6.8%) heterotopic, 1 (2.4%) ovarian and 2 (4.5%) cornual pregnancies. Of 38 tubal EP one was twin and one was triplet. Laparotomy was performed in 23 (52%) patients, and laparoscopy in 21 (48%). In 38 (88%) salpingectomy was performed, in one (2.3%) ovarian resection, in one (2.3%) prostaglandin E₂ (PGE₂) (Upjohn, USA) was injected under laparoscopic control (14), and in three (7%) salpingostomy and coagulation of the proximal part of the tube were made.

For statistical analysis we used chi-square test.

RESULTS

Of 1059 clinical pregnancies (CP) achieved in 8083 cycles in the IVF-ET program 44 (4.1%) preg-

nancies were ectopic. In 42 (95.4%) patients the indication for IVF-ET was tubal factor, in one (2.3%) unexplained, and in one (2.3%) male factor. With regard to infertility category, the highest incidence of EP was found in patients with tubal factor infertility (5.4%), which was significantly higher than in male (0.9%) and unexplained (2.0%) infertility. In the patient with unexplained infertility the EP was ovarian. EP did not occur with other indications (Table I).

In 95% of all cycles two protocols for ovarian stimulation (hMG + hCG and GnRH-a + hMG + hCG) were used. Therefore the majority of CP resulted from ovarian stimulation using these protocols. No significant differences were found between the two protocols with regard to the incidence of EP which was 4.8% and 3.1% respectively (Table II).

We used transcervical intratubal ET only 36 times in patients with unexplained infertility and in those with endometriosis AFS stage I and II, with intact tubes. Five CP were achieved and no EP occurred. At ET we used two positions. The patients in whom ET in intrauterine cavity was performed were divided into two groups. In group A we transferred embryos in chest-knee position in patients with anteverted uterus, and in lithotomy position in patients with retroverted uterus. In group B all embryos were transferred in lithotomy position regardless of the position of the uterus. The incidence of EP was 26% and 17% respectively. The difference was not significant (Table III).

The efficient outcome of the IVF-ET program also depended on the number of embryos transferred. The transfer of one embryo resulted in 147 CP and 7 (4.7%) EP, the transfer of two embryos resulted in 235 CP and 14 (5.7%) EP, and the transfer of three embryos resulted in 677 CP and 23 (3.4%) EP. The incidence of EP did not correlate with the number of embryos transferred (Table IV).

Pregnancy was established with serum beta hCG determination 17 days after ET. The initial beta

Table I. Incidence of EP According to Indication for IVF

Indication	CP No.	EP	
		No.	%
Tubal	784	42	5.4
Male	102	1	0.9
Unexplained	42	1	2.0
Endometriosis	55	0	0
Others	76	0	0
Total	1059	44	4.1

Table II. Incidence of EP According to Stimulation Protocol

Stimulation protocol	CP No.	EP	
		No.	%
CC + hMG + hCG	30	0	0
hMG + hCG	729	35	4.8
GnRH + hMG + hCG	288	9	3.1
GH + GnRH + hMG + hCG	4	0	0
Natural cycle	8	0	0
All pregnancies	1059	44	4.1

hCG value in patients with EP was 157 ± 143 mIU/ml which was significantly lower than in patients with normal singleton pregnancy in whom the initial beta hCG value was 408 ± 148 mIU/ml (Fig. 1).

DISCUSSION

It has been suggested that ovarian stimulation may be responsible for the occurrence of EP after IVF-ET, particularly the stimulation with CC. Cohen (15) found a marked decrease in the incidence of EP since CC stimulation was abandoned, while other studies (6,16) could not confirm this observation. In the present study the number of CC stimulated cycles was extremely low; therefore we could not make an appropriate comparison with other protocols used. Likewise, the opinions on the E_2 level being a risk factor for EP are also controversial (6,17). ET procedure is supposed to affect the occurrence of EP in many ways. ET into the uterine fundus is supposed to trigger pathologic contractions of the uterus leading to the expulsion of the embryos into the tubes. Some authors (2,18) have proved that with a fixed-length transfer site (55 mm from the external os) the same pregnancy rate is achieved as with transfer catheter touching the uterine fundus, but with significantly lower incidence of tubal EP. However, with depositing embryos in the lower uterine cavity there exists a danger of cervical pregnancy (19). The opinions on the volume of culture medium are not uniform either (9,17). Some

Table III. Incidence of EP According to the Type of ET

Type of ET	CP No.	EP	
		No.	%
Transcervical intratubal	5	0	
Chest-knee	738	26	3.5
Lithotomy	316	18	5.7
Total	1059	44	4.1

Table IV. Incidence of EP According to the Number of Embryos Transferred

No. of embryos	CP No.	EP	
		No.	%
1	147	7	4.7
2	235	14	5.7
3 and more	677	23	3.4
Total	1059	44	4.1

authors (15,20), however, consider the technique of ET (a patient's position, type of catheter and volume of culture medium) to have absolutely no effect on the outcome of ET. The latter fact was confirmed in our study as well. Regardless of the cause and the mechanism involved in the passage of embryos into the tubes, we observed that the occurrence of EP depended solely on the damaged tubes, not capable of contractions in the direction of the uterus favoring implantation in the tube. Our observation that tubal pathology was the main reason for the occurrence of EP is in agreement with the results of other studies (6,21-23). We presume that in cases of unexplained infertility tubal factor was most likely the underlying pathology, which could not be diagnosed with routine diagnostic procedures such as HSG and laparoscopy, but would very likely be detected with tuboscopy. The patients with unexplained infertility underwent several cycles of ovarian stimulation and intrauterine inseminations prior to IVF.

The role of routine preventive salpingectomy is debatable, and would mean overtreatment in 89% (6). It does not prevent the occurrence of cornual pregnancy, some patients conceive during the procedures, and it may impair the ovarian vascularization. It is therefore recommended in patients with voluminous hydrosalpinges (6), or in those with failed reconstructive surgery for distal tubal disease (3).

The higher the number of embryos transferred the higher the pregnancy rate (23), but in agreement with other authors (24) we found that the incidence of EP does not increase. However, multiple ET may lead to heterotopic pregnancy, the incidence of which is much higher in assisted reproductive techniques than in spontaneous conception (5) and represents a major diagnostic problem.

Early diagnosis of EP is of extreme importance as it enables minimally invasive laparoscopic surgery, nowadays widely used (25). Beta hCG has a high predictive value in the early diagnosis of EP, as on day 9 after ET already, and particularly on day 17

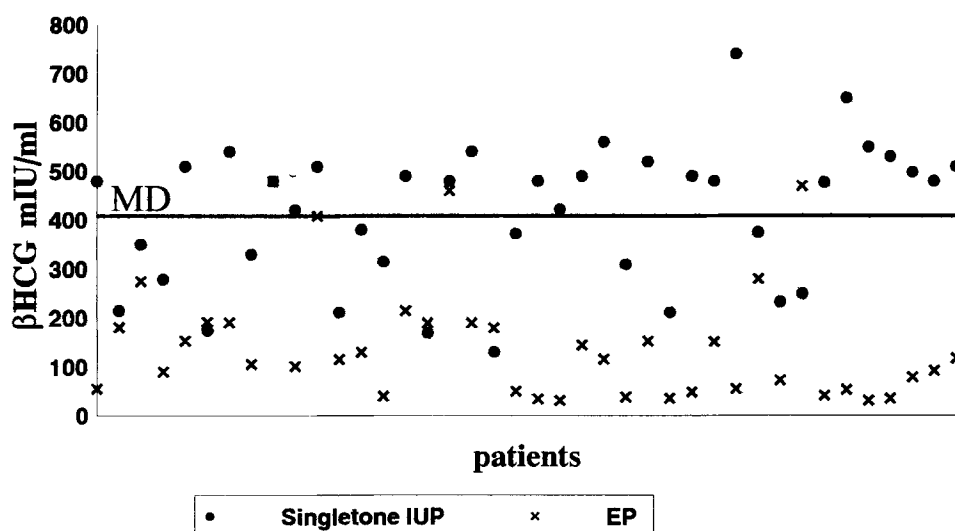


Fig. 1. β hCG values 17 days after ET.

after ET, normal singleton intrauterine pregnancy (IUP) can be distinguished from a pathologic one (26).

Using high-resolution vaginal ultrasound probes and taking into account the discriminatory zone for beta hCG (for a certain ultrasound device) the early diagnosis of pathologic pregnancy, EP included, can be made (27). Salpingectomy is the method of choice when EP occurs after IVF due to potential risk of repeated EP in next cycles (28). A major dilemma remains the approach to the contralateral tube. Bilateral salpingectomy or proximal occlusion should be considered in patients with bilateral damaged tubes and failed reconstructive surgery.

CONCLUSIONS

EP can complicate the IVF-ET procedure. The main risk is tubal infertility with or without previous tubal surgery. The low initial value of beta hCG has a strong predictive value in the diagnosis of EP.

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