

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

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Kissler S, Wiegratz I, Kohl J, Rody A, Gaetje R

Kaufmann M

J. Reproduktionsmed. Endokrinol 2006; 3 (6), 387-389

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Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



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Repeated Ectopic Pregnancy After ICSI Therapy and Embryo Transfer – A Case Report and Literature Review

S. Kissler¹, I. Wiegratz¹, J. Kohl¹, A. Rody², R. Gaetje², M. Kaufmann²

The risk of ectopic pregnancy is increased following IVF/ICSI embryo transfer treatment. Established risk factors include the number of embryos transferred, length of the uterine cavity, fluid volume and the extent of tubal damage in cases of tubal sterility. Hence, ectopic pregnancies following IVF treatment are more common than after ICSI treatment. We report a rare case of two consecutive ectopic pregnancies in one patient following ICSI treatment. Since pathology of the fallopian tubes could be excluded, a risk factor for the development of an ectopic pregnancy seems to be a difficult embryo transfer with a consecutive arousal of uterine contractions mainly in cervico-fundal direction which might have lead to an expulsion of embryos into the fallopian tubes. To avoid a further ectopic pregnancy in forthcoming cycles we performed bilateral complete salpingectomy during laparoscopy in that patient. J Reproduktionsmed Endokrinol 2006; 3 (6): 387–9.

Key words: consecutive ectopic pregnancy, IVF/ICSI and ET, uterine contractility, bilateral complete salpingectomy

The incidence of an ectopic pregnancy varies in a range between 0.3 % and 1.4 % of all pregnancies [1–3]. An increased incidence of ectopic pregnancies up to 5 % after *in vitro* fertilization (IVF) and embryo-transfer (ET) is a well-known phenomenon [4, 5]. Hence, the first pregnancy achieved by IVF resulted in an ectopic pregnancy [6].

Analysing recent years in Germany, a statistically higher rate of ectopic pregnancies after IVF can be observed compared to those following an intracytoplasmic sperm injection (ICSI) treatment (2.85 % vs. 1.80 %, 2004) [7]. It can be concluded that pathology of fallopian tubes after pelvic inflammatory disease (PID) or endometriosis might be the main reason for an ectopic pregnancy after IVF therapy. Although there is evidence that the risk for a repetition of an ectopic pregnancy is estimated in a range of 10–20 % [2], there are only 2 case reports about a second, repeated ectopic pregnancy following an IVF-ET treatment in the literature [8, 9]. In one case [9], the first two ectopic pregnancies were conceived spontaneously, the third ectopic pregnancy was achieved by IVF, which was indicated after tubal surgery.

Therefore, we report a very rare case of a repeated ectopic pregnancy in the same patient in two IVF cycles.

Case Report

The 31-year old patient and her 38-year old husband were suffering from primary infertility for 3 years. Andrologic examination revealed a syndrome of oligo-astheno-teratozoospermia (OAT syndrome; concentration: 15.5 mio/ml, motility a+b: 34 %, morphology: 8 % normal forms).

In the female, diagnostic laparoscopy during sterility work-up revealed minimal endometriosis rAFS-class I

with patency of fallopian tubes proven by dye-pertubation. The patient did not report any endometriosis-related symptoms. Her cycles and hormone values were regular. After 2 intrauterine inseminations with difficult passage of the cervical canal that additionally revealed a further impairment of sperm parameters, we indicated ICSI treatment.

The first ectopic pregnancy was achieved by the second ICSI treatment cycle. During this cycle, hormonal stimulation was performed in a long protocol using Synarela® nasal spray (Pharmacia) beginning on day 20 of the menstrual cycle followed by ovarian stimulation on day 2 with 300 IU recombinant FSH which was reduced to 225 IU FSH (Gonal-F®, Serono, Unterschleißheim). After 11 days of ovarian stimulation, ovulation was typically induced (10.000 IU HCG, Choragon®, Ferring-Arzneimittel, Kiel) and 36 hours later 9 oocytes were retrieved during follicle aspiration. After 2 days, an uncomplicated ET of 2 embryos (4-cell-stage) could be performed since cervical dilatation up to Hegar 12 was performed in the pre-treatment cycle. For luteal supplementation, a combination of Choragon® 1500 IU (Ferring-Arzneimittel Kiel) for three times and daily Crinone® 8 % vaginal gel (Serono, Unterschleißheim) was chosen. After 14 days, the patient presented with a positive pregnancy test, after 25 days HCG has increased to a level of 4650 IU/l without showing an intrauterine pregnancy. Progesterone values are not usually measured in our IVF unit. The patient did not have any clinically relevant symptoms, but transvaginal ultrasonographic examination was suspicious for an ectopic pregnancy in the right fallopian tube. In a first step, since the patient was asymptomatic, 50 mg methotrexate was administered intravenously (Methotrexat®, Medac, Hamburg). After 3 days, laparoscopic intervention was mandatory since the patient experienced severe abdominal pain. During surgery, fimbrial ectopic pregnancy of the right tube was documented which easily could be removed. The contralateral left tube was without any pathology. The patient recovered soon after surgery and the postoperative HCG controls showed a regular decline.

After a break in infertility treatment of 3 months, three cryo-ET cycles and one new ICSI treatment cycle were unsuccessful.

The 4th ICSI treatment cycle was followed by the 2nd ectopic pregnancy: this time, ovarian stimulation was per-

Received: September 1, 2006; accepted after revision: September 13, 2006.

From the ¹Gynecologic Endocrinology and Reproductive Medicine and the ²Department of Obstetrics and Gynecology of the Johann Wolfgang Goethe-University, Frankfurt/Main.

Correspondence: Stefan Kissler, MD, Gynecologic Endocrinology and Reproductive Medicine, Dept. OB/GYN, Johann Wolfgang Goethe-University, D-60590 Frankfurt/Main, Theodor-Stern-Kai 7, Germany; e-mail: stefan.kissler@kgu.de

formed using a short protocol with Synarela® nasal spray beginning on cycle day 1 followed by administration of Menogon® (Ferring Arzneimittel, Kiel) 3 ampoules/day and Gonadotropin (Serono, Unterschleißheim), 150 IU/day, beginning on cycle day 3. This protocol was chosen because during the third stimulation cycle low response of the ovary was observed. After 10 days of stimulation, ovulation was induced in the same way as described before and 8 oocytes were retrieved 36 hours later. Two days after oocyte retrieval, ET of 3 embryos (4- and 2-cell-stage) was performed. During this ET, cervical passage was again aggravated and the use of a tenaculum was necessary. Luteal substitution was again performed using a combination of Crinone® 8 % vaginal gel and Choragon® 1500 IU for three times.

Twenty-two days after ET the HCG-level in the serum of the patient was 1559 IU/l without any evidence of an intrauterine pregnancy using transvaginal ultrasonography. Progesterone values were not detected. Having discussed the situation with the patient, laparoscopy was again performed. The patient wanted us to remove both fallopian tubes if another ectopic pregnancy was diagnosed in order to continue ICSI treatment without any risk of experiencing an ectopic pregnancy again.

During surgery, an isthmic ectopic pregnancy of the left fallopian tube was diagnosed (Figs. 1, 2). This time, the

right fallopian tube could be described as normal. Both tubes were removed laparoscopically at the utero-tubal junction (Fig. 3).

The patient recovered quickly and the HCG decline was normal. The patient is still willing to undergo a fifth ICSI cycle.

Literature Review and Discussion

The most important etiologic factors for an ectopic pregnancy are pelvic inflammatory disease (PID), abdominal surgery or surgery of the pelvis, the previous use of an IUD or finally IVF/ET treatment [1, 2, 10]. Hence, even the first pregnancy achieved by IVF resulted in an ectopic pregnancy [6]. Some studies describe a reduced volume of the uterine cavity as a reason for ectopic pregnancies [11] but in most cases the extent of tubal damage should be regarded as responsible for an increased incidence of ectopic pregnancies.

IVF/ICSI treatment might additionally result in a heterotopic pregnancy (simultaneous appearance of intrauterine and ectopic pregnancy). Without a method of assisted reproductive techniques this event is very rare, after IVF/ICSI treatment, a heterotopic pregnancy must be considered in a symptomatic patient.

Although the etiology of an increased incidence of ectopic pregnancies complicating IVF/ICSI treatment might be explained by several factors (number of embryos transferred, volume and applied pressure of culture medium during ET and tubal pathology in IVF patients), some recent studies have described the influence of uterine contractility during ET as another etiologic factor.

First experimental examinations concerning ET have clearly shown an expulsion of embryos into the vagina [12, 13]. Following mock embryo transfer in humans an expulsion of methyleneblue solution into the vagina was documented in 57 % of the patients [14] and in another study expulsion of X-ray contrast medium into cervix and vagina was documented in 21 % of cases [15]. Interestingly, this study additionally showed an expulsion of the contrast medium into fallopian tubes in 38.2 % and gave evidence for the first time that ET might be associated with a higher risk of a tubal implantation of embryos.

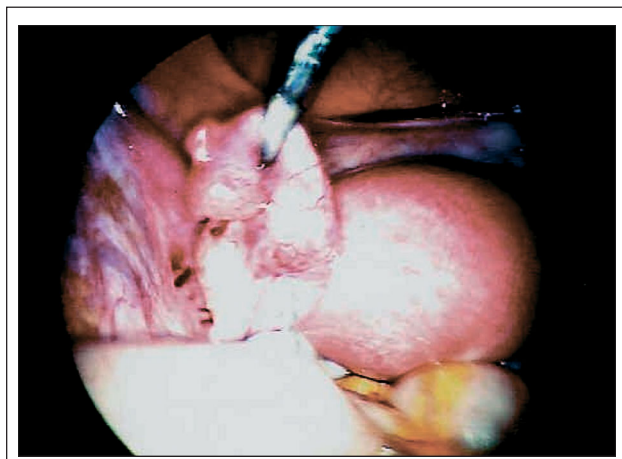


Figure 1. Ectopic pregnancy in the isthmic part of the left fallopian tube

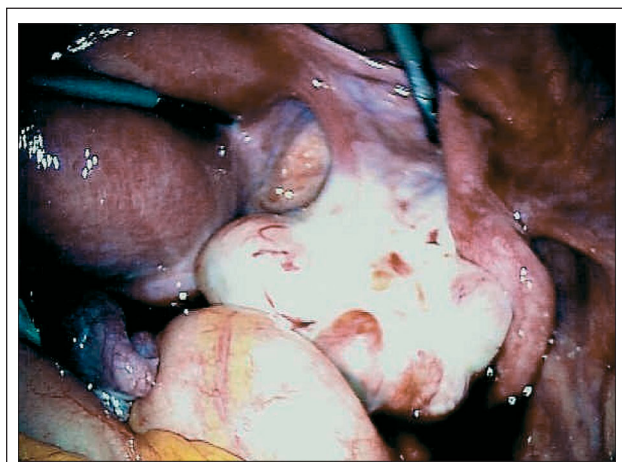


Figure 2. Normal contralateral right tube that was operated 14 months before because of a fimbrial ectopic pregnancy

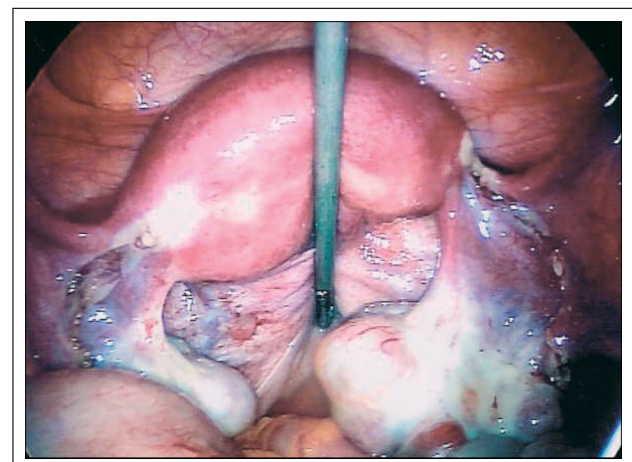


Figure 3. Postoperative site: bilateral complete salpingectomy in the utero-tubal junction

Other studies show that the phenomenon might be physiologic and the embryo gets into contact with the fallopian tube via retrograde transport, while healthy tubes – as in cases of ICSI patients – have the ability to return the embryos back to the uterine cavity [16]. Further studies gave evidence that the tubal status (i.e. after PID) is the main risk factor for ectopic pregnancy [17, 18].

An aggravation of the ET technique might be considered as a risk factor for an ectopic pregnancy after IVF/ICSI treatment, too. The use of a tenaculum might arouse uterine contractions especially in the subendometrial myometrium. Lesny et al reported a significant increase in uterine cervico-fundal (retrograde) contractility documented by transvaginal ultrasound after the insertion of a tenaculum. The increase of a retrograde contractility pattern should be regarded as another risk factor for an ectopic pregnancy besides the tubal status [19].

This is supported by the observation by Fanchin et al that an increased frequency of subendometrial contractions during an aggravated ET procedure is significantly associated with reduced pregnancy rates and that myometrial contractions should be avoided by using a gentle, atraumatic transfer technique. In this study, cervico-fundal (retrograde) peristalsis prevails in 64 %, antegrade peristalsis was only observed in a minority of subjects [20].

Another etiologic factor that should be considered in this discussion is the disease endometriosis, which was diagnosed in our patient during sterility work-up. Although it is not known that a minimal spread of pelvic endometriosis without the destruction of the tubo-ovarian functional unit – as in our patient – might serve as a risk factor for an ectopic pregnancy, there are some impressing examinations in patients with endometriosis about the change in utero-tubal transport capacity on the basis of impaired uterine peristalsis [21, 22]. In patients with endometriosis, a significant dys- and hyperperistalsis compared to healthy controls can be observed in hysterosalpingoscintigraphy (HSSG) which is the only reliable method for evaluating utero-tubal transport capacity. Adenomyosis uteri, which shows a high prevalence in patients with endometriosis and affects the subendometrial myometrium, which is responsible for physiologic uterine contractility, might serve as the underlying condition for the impairment of utero-tubal peristalsis [23, 24].

In our opinion, the aggravation of the ET procedure serves as the most important etiologic risk factor for the repeated tubal pregnancy in our patient. Although the first ET that lead to the first ectopic pregnancy was uncomplicated, the patient underwent a cervical dilatation in the previous cycle since two intrauterine inseminations were aggravated. Nevertheless, the patient reported pain during the ET procedure. All further ET in the described patient were estimated as very difficult and could only be performed with the use of a tenaculum.

Our case report and the review of the literature should therefore stress the importance of a gentle, atraumatic embryo transfer technique.

Aggravation of ET should be considered the main risk factor for the repeated ectopic pregnancy in our patient.

The prophylactic bilateral removal of the fallopian tubes in their utero-tubal junction is in our opinion the only way to avoid another ectopic pregnancy after ICSI treatment.

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