Two consecutive ectopic pregnancies after in-vitro fertilization and embryo transfer. Case report

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Summary

Ectopic pregnancy is a known complication of in vitro fertilization and embryo transfer (IVF/ET). The overall incidence of ectopic pregnancy after IVF is 4.4-5.8% of clinical pregnancies. The risk factors associated with ectopic pregnancies are complex. We present a patient with two consecutive ectopic pregnancies after IVF/ET.

Key words: Ectopic pregnancy; IVF.

Introduction

Ectopic pregnancy is a known complication of in vitro fertilization and embryo transfer (IVF/ET). The overall incidence of ectopic pregnancy after IVF is 4.4 - 5.8% of clinical pregnancies [1]. The risk factors associated with ectopic pregnancies are complex and controversial. We present a patient with two consecutive ectopic pregnancies after IVF/ET.

Case Report

A 36-year-old patient with a nine-year history of primary infertility due to severe endometriosis and damaged Fallopian tubes was referred to our center for IVF/ET. The patient had two laparotomies performed for the treatment of endometriosis. Semen analysis of the husband was normal.

In the first cycle, ovarian stimulation was achieved by human menopausal gonadotropin (HMG, Humegon; Organon Ltd, Oss, The Netherlands), started on the third day of menstruation with a dose of 300 IU daily, accompanied by gonadotropin-releasing hormone agonist (Triptorelin, Decapeptyl: Ipsen Biotech, Paris, France) administered 0.1 mg daily as of day 21 of the previous cycle. The patient was monitored by transvaginal ultrasound scans. When two follicles reached a diameter of 18 mm, 10,000 IU human chorionic gonadotropin (HCG, Pregnyl; Organon Ltd, Oss, The Netherlands) were given. Oocyte retrieval was done 36 hours after HCG administration using an ultrasound-guided transvaginal approach. Of the 20 oocytes obtained, 16 were fertilized and four embryos were transferred into the uterine cavity 48 hours after aspiration. The embryos were suspended in a < 20 µl of transfer medium in a Frydman catheter (Laboratoire CCD, Paris, France) and transferred transcervically into the uterine cavity about 10-15 mm short of the fundus. Replacement was performed in the dorsal lithotomy position and the patient was allowed to rest for two hours before discharge. Luteal support was achieved using micronized progesterone (Uterogestan, Laboratoires Besins Iscovecso, Paris, France). Fourteen days after the embryo transfer the urinary pregnancy test was positive. The first ultrasound evaluation was done two weeks later revealing an empty uterine cavity. Serum β-HCG was 2805 mIU/ml. Repeat b-HCG two days later revealed a level of 4018 mIU/ml. The patient was diagnosed to have an ectopic pregnancy based on an increase in b-HCG and an empty uterine cavity. She was treated successfully with intramuscular methotrexate.

The patient presented eight months later for a repeat IVF cycle. She was counseled about surgical removal of her tubes prior to treatment, however, she refused. In the second IVF cycle, four embryos were transferred, however, this time the transfer was done under ultrasound guidance. The embryos were suspended in a < 20 µl of transfer medium in a Frydman catheter (Laboratoire CCD, Paris, France). Under the guidance of abdominal ultrasound, the tip of the catheter was introduced into the mid-cavity of the uterus and the transfer column was slowly deposited there. β-HCG done 12 days after transfer was 132 mIU/ml. The patient was followed up with serial β-HCG and ultrasound and was diagnosed again as a case of ectopic pregnancy based on a rising b-HCG titer and an empty uterus. She was treated successfully with methotrexate after she refused surgical treatment.

Discussion

Ectopic pregnancy is a known complication of IVF/ET. The incidence of ectopic pregnancy after IVF/ET is 3- to 5-fold higher than natural cycles [2], with an estimated incidence of 4.4-5.8 % [1].

Data on the risk factors associated with ectopic pregnancies are conflicting and complex. Pre-existing tubal pathology seems to be the main risk factor for ectopic pregnancies [2, 3]. Dubuisson et al. found that the incidence of ectopic pregnancy in patients with bilateral salpingectomy was 4% as compared to 14.2% in patients who had hydrosalpinx and 9.9% in patients with pathological but patent tubes [3]. In the present case, tubal damage seems to be the main predisposing factor for the ectopic pregnancies. A prior ectopic pregnancy as a risk for developing another one remains controversial.

Revised manuscript accepted for publication September 18, 2002

Marcus and Brinsden could not identify any risk factor related to prior ectopic pregnancy *per se* [2], while Karande *et al.* identified prior ectopic pregnancy as the main risk factor for developing ectopic pregnancy after IVF/ET [4]. Whether the first ectopic pregnancy our patient had would have predisposed her for the second one is not clear. Studies with a large number of patients that would evaluate the risk of developing a second ectopic pregnancy after having the first one after IVF/ET are needed.

Various authors have incriminated the technique of embryo transfer for the ectopic preganacies seen in IVF/ET. Marcus and Brinsden showed that ectopic pregnancy was associated with a high transfer volume [2]. The volume of transfer medium was gradually decreased after the report of Knutzen et al. which demonstrated that as a little as 40 µl of radio opaque fluid injected into the uterine cavity could reach the Fallopian tubes in 38% of patients, suggesting that the chance of the embryo being carried into the tube immediately after transfer is high [5]. Because most ectopic pregnancies occur in patients with damaged tubes, it seems likely that the embryo(s) that reach the Fallopian tubes after embryo transfer, is not transported back to the uterine cavity because of tubal dysfunction. In our patient, using a low transfer volume of < 20 µl did not prevent the occurrence of ectopic pregnancies. Yovich *et al.* reported a higher incidence of ectopic pregnancies with placement of embryos high in the uterine cavity within 5 mm of the fundus [6]. In our patient, the first embryo transfer was done in the mid-cavity 10-15 mm from the fundus. Although the second embryo transfer was done under ultrasound guidance with the embryos deposited in the mid-cavity of the uterus, the pregnancy ended as an ectopic. This is in accordance with the findings of Sieck *et al.* that showed that ultrasound-guided embryo transfer does not prevent ectopic pregnancies after IVF [7].

The role of different stimulation protocols as a risk factor for ectopic pregnancies is controversial. Some authors did not find any evidence of an association between ectopic pregnancy and different ovarian stimulation protocols [2, 3]. However, Cohen *et al.* reported an increased risk of ectopic pregnancies with the use of clomiphene citrate [8]. They suggested that the reason for this is due to abnormal uterine contractility and altered tubal motility as a result of stimulation might lead to an altered hormonal environment which changes the anti-effect of clomiphene citrate. In addition, Fernandez *et al.* suggested that ovarian oestrogenic uterine and tubal contractility and thus favors migration of correctly placed embryos into the tubes [9].

It is still unclear why embryos placed in the uterine cavity would subsequently reach the Fallopain tubes and implant there. Tubal pathology seems to be the main risk factor. In order to prevent recurrence, it would seem to be more appropriate to treat ectopic pregnancy after IVF with salpingectomy rather than with medical treatment. However, before applying such a recommendation it is important to know the incidence and risk factors of recurrent ectopic pregnancies after IVF/ET.

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Successful treatment with carbimazole of a hyperthyroid pregnancy with hepatic impairment after propylthiouracil administration: a case report

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Summary

We report the case of a 27-year-old woman with hyperthyroidism during pregnancy. Antithyroid treatment with propylthiouracil (PTU) resulted in elevated hepatic enzymes and after the 12th week of pregnancy tratment was changed to carbimazole (CBZ). The remaining pregnancy, delivery and follow-up period were uneventful for the mother and her offspring. Antithyroid treatment during pregnancy should allow the use not only of PTU but also of CBZ and methimazole.

Key words: Thyrotoxicosis; Pregnancy; Propylthiouracil; Hepatotoxicity; Carbimazole.

Introduction

Hyperthyroidism during pregnancy is rare - encountered in one out of 1,000-2,000 pregnancies [1, 2]. Treatment is usually with propylthiouracil (PTU), which is preferred over the other thionamides. We hereby present our experience with antithyroid treatment during pregnancy, with the particularity that PTU resulted in elevated hepatic enzymes and had to be replaced.

Case report

A 27-year-old woman was referred for further management during the 12th week of her first pregnancy with untreated hyperthyroidism and elevated hepatic enzymes. Past medical history was remarkable for one stillbirth due to anencephaly. The patient was diagnosed with thyrotoxicosis six months before her referral and PTU 300 mg/day was administered, however, at the beginning of her current pregnancy elevated aminotransferases were noted, necessitating tapering of PTU to 150 mg/day and finally complete withdrawal of antithyroid therapy.

Physical examination disclosed an anxious young woman with tachycardia (heart rate: 120/min). Tremor and neck swelling were evident but no exophtalmos or bruits on cardiac and neck auscultation were noted.

The laboratory work-up on admission was notable for elevated aminotransferases (AST: 78 U/l and ALT: 151 U/l) and gamma-glutamyl transpeptidase (65 U/l), normal bilirubin at 0.5 mg/dl and normal blood coagulation tests (APTT 40 sec, PT: 12/12 sec and INR: 1). The viral hepatitis panel was negative. Thyroid hormones were elevated (total thyroxine: 406 nmol/l, free thyroxine: 71.2 pmol/l, total triiodothyronine: 8.3 nmol/l, thyrotropin: 0.02 μIU/ml, anti-thyroperoxidase autoantibodies: 776 IU/ml, anti-thyroglobulin autoantibodies: 2000 IU/ml). Serum thyrotropin receptor antibodies were positive at 31 mIU/ml.

Ultrasound imaging studies disclosed an enlarged thyroid with diffuse parenchymal unhomogeneity in the mother and a normal fetus corresponding to the gestational age.

The patient - after normalization of the hepatic enzymes - was offered the option of thyroidectomy. However, she opted, with informed consent, to be administered carbimazole (CBZ) at 10 mg/day. The clinical response was good and normalization of hepatic abnormalities was observed within ten days. The pregnancy progressed uneventfully; the mother remained euthyroid while the evaluation of the fetus with ultrasound did not detect any abnormalities. A healthy euthyroid baby was born, at term, after a cesarean delivery. Antithyroid treatment of the mother was successfully pursued after delivery, while the baby remained euthyroid and developed normally.

Discussion

Since untreated or incompletely treated maternal hyperthyroidism in the first trimester may lead to maternal complications (such as congestive cardiac failure) and to an increase in the rate of fetal congenital anomalies, treatment with antithyroid medications is strongly advised [3].

Currently PTU is preferred over CBZ or methimazole (MTZ) in the treatment of hyperthyroidism during pregnancy. The preference for PTU is based on experimental studies that showed lower transplacental passage and higher binding to albumin of PTU compared to MTZ [4], reports of a rare skin condition (aplasia cutis congenita, which occurs spontaneously in approximately 1 in 2,000 births [5, 6]) and congenital malformations [7] associated with MTZ use during pregnancy. Although skin abnormalities in the newborn have been linked to maternal MTZ use during pregnancy, this association may be fortuitous [6].

Experimental work has shown that MTZ and CBZ have a higher rate of biliary excretion than PTU [8]. Apparently, MTZ and CBZ are more effectively oxidized in

Revised manuscript accepted for publication September 26, 2002

the liver, resulting in lower bioavailability in hepatocytes and a lower potential for hepatotoxicity compared to PTU. The incidence of antithyroid drug-associated hepatotoxicity is approximately less than 0.5% [9]. PTU-associated hepatotoxicity occurs more commonly in women and presents with a wide range of findings from hepatocellular inflammation to submassive hepatic necrosis [10]. An autoimmune reaction to PTU has been suggested as a cause of its toxicity [10]. Therapy with PTU should be discontinued upon recognition of toxicity, since up to 25% of affected patients may progress to fulminant and fatal hepatic failure [10]. MTZ use has also been associated with hepatic complications, though much rarer. Cholostasis has followed MTZ treatment in very few patients, although three deaths have been reported [10, 11]. Sclerosing cholangitis following MTZ treatment has also been described [12]. If side-effects appear with antithyroid treatment, CBZ or MTZ can be substituted for PTU and vice versa, although cross-sensitivity to these drugs may occur [13]. As a matter of fact, the rate of untoward cross-reactions between CBZ and PTU was 15.2%, in a study of 1,256 treated patients with hyperthyroidism [14].

Our patient presented with thyrotoxicosis during pregnancy. The initial treatment with PTU resulted in hepatic enzyme elevation and prompted a change in antithyroid medication. CBZ was administered with excellent response. Thus, in analogous cases antithyroid medication choice can also include other thionamides with a good margin of safety [3].

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