

Case Report

Heterotopic Pregnancy after Assisted Reproductive Techniques: Case Reports

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Abstract

Heterotopic pregnancy (HP) is the simultaneous occurrence of intra- and extrauterine pregnancies. It is a rare event in spontaneous pregnancies with an incidence of less than 1:15000, however the frequency has increased to 1% in accordance with the widespread use of assisted reproductive techniques (ART).

The pre-operative diagnosis of this condition is generally difficult and it would be life threatening for mother and the intrauterine pregnancy. In this report, we present three cases of HP following ART. All cases underwent a standard long protocol and embryo transfers (ET) were performed 48 hours after oocyte retrievals. Finally, two viable intrauterine gestations ended in miscarriages and the third resulted in the delivery of a healthy infant.

The possibility of a heterotopic pregnancy following tubal pathologies, endometriosis and pelvic adhesions should be considered by gynecologists during IVF procedures. Moreover by implantation of a single embryo, the incidence of this risky condition will be dramatically reduced.

Keywords: Ectopic Pregnancy, Assisted Reproductive Techniques, *In vitro* Fertilization, Embryo Transfer

Introduction

Heterotopic pregnancy (HP) is the co-existence of intra- and extrauterine gestations (1). Although extremely rare in a spontaneous pregnancy with an estimated rate from 1:15000 to 1:30000, nowadays its incidence has increased to 1:100 with the widespread use of assisted reproductive techniques (ART) or ovulation induction (2).

HP is a life threatening condition for both the mother and the fetus (3). The probabilities of spontaneous abortions are higher in combined pregnancies than intrauterine-only pregnancies (4, 5). These complicated pregnancies are diagnostic and therapeutic challenges to infertility practitioners (3, 6). Serum serial β hCG concentrations and ultrasound evidences diagnosis of an intrauterine pregnancy might obscure typical signs of an ectopic pregnancy (EP) (1). This delay in diagnosis leads to maternal complications such as tubal rupture and hypovolemic shock which might be fatal (7, 8). Therefore, confirmation of an intrauterine pregnancy is not a reliable indicator to dismiss an extrauterine pregnancy.

With respect to the high incidence of HP following *in vitro* fertilization/embryo transfers (IVF/ET) and also the possibility of a missed EP diagnosis

with increased remarkable consequences, special attention to HP issue is essential in all IVF cycles in order to preserve a viable intrauterine pregnancy and avoid maternal mortality through timely intervention.

In this report, we present three cases of HP following ART.

Case Reports

Case 1:

A 33 year-old woman, nulligravida 0, married for the second time, was admitted to our IVF unit with a 13 year history of primary infertility. Past medical history indicated a history of appendectomy and her history was negative for pelvic inflammatory disease (PID), previous EP, venereal disease or intrauterine device usage.

A recent ultrasound demonstrated an endometrioma cyst with an approximate diameter of 21 mm in the left ovary accompanied by some periadnexal adhesions and a submucosal myoma which measured 13×9 mm in the posterior wall of the uterus. For the first time, the patient underwent an agonist long protocol. On the 10th day of stimulation, five mature oocytes were collected by vaginal ul-

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trasound monitoring. Four oocytes were fertilized after insemination and 2, four-cell two, 4-cell stage embryos were transferred into the uterus using labotect catheter. The luteal phase was supported by daily intramuscular injections of progesterone for two weeks. Initial vaginal sonographic examination performed 32 days after ET demonstrated one intrauterine gestational sac with a fetal pole and heart beat at seven weeks of gestation.

The patient was hospitalized six days later (38 days after ET), with the chief complaint of low abdominal pain which began two hours prior to her admission. She was hypotensive with a hemoglobin concentration of 5 g/dl and a plasma β hCG level at this stage of 6000 IU/l. A repeat ultrasound scan confirmed a viable intrauterine gestation (eight weeks gestation) and an echogenic mass in the right tube which indicated an EP.

An emergency laparotomy was performed and the ruptured right tubal pregnancy removed. The intrauterine pregnancy continued until a transvaginal ultrasound two months following surgery revealed a missed abortion of an intrauterine pregnancy.

Case 2:

A 37 year-old woman, nulligravida 0, with an 11 year history of primary infertility, underwent an IVF procedure at our infertility center. She had a prior failed intrauterine insemination (IUI) attempt two years prior to her admission. During the previous treatment a laparoscopic myomectomy had performed with the removal of a number of adhesions in the left ovary.

The patient underwent a standard long protocol. Oocyte retrieval was performed on day 15 of the cycle which resulted in the recovery of five mature oocytes. Subsequently, four oocytes were fertilized. At 48 hours after ovum pickup three embryos (two, 4-cell and one, 5-cell) were transferred to the uterus transcervically with the use of a labotect catheter. Luteal support was performed by intramuscular administration of daily progesterone for two weeks.

The first transvaginal scan performed 24 days after ET demonstrated a gestational sac in the uterine cavity (5-6 weeks gestation). Additional findings were the existence of enlarged ovaries and pelvic-free fluid which suggested an ectopic pregnancy. Therefore, serial β hCG levels and ultrasound monitoring were suggested.

One week later, the patient was referred to the hospital with severe lower abdominal pain. The second vaginal sonography revealed enlarged ovaries with small amounts of fluid and blood in the cul-de-sac. A suspicious mass was observed between the

uterus and right ovary. These findings indicated an ectopic pregnancy together with an intrauterine gestational sac of six weeks.

Laparoscopy with right salpingectomy was performed the following day. At this stage, the luteal phase was supported with both intramuscular and intravaginal progesterone administration. Two weeks after surgery, transvaginal sonography revealed a gestational sac without a heart beat and with two weeks growth retardation, which resulted in a miscarriage.

Case 3:

A 25 year-old woman, nulligravida 0, with a four year history of primary infertility and diagnosis of unexplained infertility underwent a second IVF procedure at our institution.

A standard long agonist protocol was initiated and ultimately two embryos were transferred into the uterus. The first ultrasound was performed 32 days after ET which demonstrated a viable intrauterine pregnancy of 6.5 weeks gestation. Additional findings demonstrated the existence of an echogenic mass measuring 48×25 mm with free fluid in the cul-de-sac and peri-left ovary, which suggested the possibility of HP.

After two days, she presented to the hospital with complaints of acute abdominal pain and peritoneal irritation. After admission, severe vaginal bleeding commenced. A repeat transvaginal ultrasound revealed a ruptured left fimbria pregnancy with massive free fluid in the cul-de-sac and a seven week intrauterine pregnancy with a normal heart rate was confirmed.

An emergent laparotomy with left salpingectomy was performed and she had a non-complicated post-operative course. The intrauterine pregnancy proceeded uneventfully and she had a cesarean delivery at 34 weeks of gestation due to a premature rupture of the membranes and breech presentation which resulted in the delivery of a healthy 1850 g male infant.

Discussion

HP is an uncommon obstetric event in spontaneous pregnancies estimated at approximately one per 15000-30000 pregnancies (2). Many predisposing factors including: pelvic inflammatory disease, salpingitis, endometriosis, pelvic surgery, uterine malformations and a history of ectopic pregnancy all lead to an increased incidence of this hazardous phenomenon (1, 2, 5, 9).

Currently, addressed to the extensive use of ART methods such as IVF and ET which have the potential for multiple pregnancies, the frequency of

this condition has increased as high as 1 % (2). The use of ovarian hyperstimulation drugs, multiple ETs, and the techniques of ET, along with previous tubal damage predisposes patients to the development of a combined pregnancy (1, 2, 5).

According to studies, the main risk factor of HP following IVF is tubal infertility (10, 11). In a retrospective review that evaluated the risk factors of HP following IVF, ten out of twelve patients had a previous history of salpingitis and one had tubal surgery due to a previous EP (5). The risk of a second EP is 2-15 times higher in women with a prior history of EP (12). It has also been suggested that unilateral salpingectomy may increase the risk of an EP on the opposite side (11).

According to a study by Strandell et al. although there is no consensus that fibroids may be a risk factor for EP following ART, however the myometrial scar may disrupt normal uterine contractions which prevents intrauterine implantation (11). Therefore, further studies need to be performed.

It is reported that HP are directly relevant to the number of transferred embryos during IVF/ET treatment (2, 13-15). Therefore a reduction in the number of transferred embryos could contribute to a decrease in the occurrence of HP (8). Both the technique and timing of ET have been implicated as risk factors for HP. Yovich et al. have noted a significantly higher rate of extrauterine pregnancies when embryos were implanted nearer to the uterine fundus rather than mid-cavity (16). According to Lesny et al., a difficult ET leads to junctional zone contractions which enhance the risk of EP. The incidence rates of EP exceed 1.5-10 times when ET is performed under difficult rather than easy conditions, in particular if is ET performed on day two compared to day three following oocyte collection (12).

Early detection of HP remains difficult in the absence of a tubal rupture (1). A normal rise in serum β -hCG levels and ultrasonography diagnosis of intrauterine pregnancy might obscure the abnormal pattern typically observed in EP. When ultrasonography reveals an intrauterine pregnancy the possibility of EP is generally ignored (1). Furthermore, the presence of ovarian hyperstimulation syndrome (OHSS) during ART might mask the EP signs in HP cases thus preventing a definitive diagnosis prior to surgery (17). Over half of all HP are recognized during emergency surgeries following tubal rupture (2).

Treatment of HP is complicated because of the co-existing intrauterine pregnancy and should be the least invasive as possible in order to achieve a good outcome for the intrauterine pregnancy. Laparo-

scopic surgery (salpingostomy or salpingectomy) is the most effective treatment in a woman diagnosed with tubal pregnancy and its safety is demonstrated during pregnancy (18, 19). Laparotomy is generally performed for life threatening cases or for occasions that can not be treated by laparoscopy (8).

As seen in these cases, tubal damage, pelvic adhesions, a history of pelvic surgeries and the high number of transferred embryos possibly are risk factors of a combined pregnancy occurrence. Ultimately, addressing recent studies that suggest a single ET would avoid multiple pregnancies without significant effect on pregnancy outcome (20, 21) therefore, special attention to this high-risk group is highly recommended before every IVF procedure in order to lessen the HP rate as a result of a single embryo replacement.

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