

Case Report

# Heterotopic Pregnancy and Hemorrhagic Shock Following Embryo Transfer of Cryopreserved-Thawed Blastocysts with Successful Outcome

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## Abstract

Heterotopic Pregnancy (HP) is a very rare entity, but due to the use of In Vitro Fertilization (IVF) techniques it is now a common complication of IVF. However, there are no literature reports of HP when a Frozen-Thawed Embryo Transfer (FET) of blastocysts is performed. In stimulated cycles, one or two embryos are replaced usually on days 3-5 after follicular aspiration and the rest are frozen for future FET attempts. This adds much to the cumulative pregnancy rate for the particular cycle, especially if the frozen embryos are blastocysts. However, there are no reports of HP with FET of blastocysts, although HP with FET of 3 day embryos has been previously reported.

We report a case of a 35-year old patient, 7-weeks pregnant after the FET of two thawed blastocysts, who presented into the emergency room in a state of a hemorrhagic shock, with no vaginal bleeding. At her previous exam, at 5+3 weeks of pregnancy, one gestational sac in the uterus was visualized. At admission, Transvaginal Ultrasound (TVU) revealed an adnexal mass on the right side of the lower abdomen, an abdominal cavity filled with large amount of free fluid, and a two-millimeter embryo with a positive heart rate in the uterus. An emergency laparotomy and right salpingectomy were performed, and HP was confirmed. The intrauterine pregnancy continued without any complications, and resulted in a vaginal delivery of a live-born child, at full term. Caution should be exerted when two cryopreserved and thawed blastocysts are transferred, because there is the possibility of a HP.

**Keywords:** FET; Blastocyst; Heterotopic pregnancy; Tubal rupture; Hemorrhagic shock introduction

## Introduction

In HP, one or more intrauterine pregnancies coexist with ectopic ones. Although it is a rare occurrence in spontaneous conception, with a reported incidence of 0.08%, with Assisted Reproductive Technology (ART) the incidence rose to approximately 1%-5% [1,2]. Several aetiological factors could be pointed out in the pathophysiology of the higher incidence of HP in ART such as: transfer of excessive numbers of embryos; malformed ovum quality with low implantation potential; embryo transfer technique with unintended injection of embryos somewhere else than the uterine cavity including rarely possible uterine perforation; tubal ciliary dysfunction following elevated progesterone level; retrograde way of embryos into the tube due to hydrostatic forces; increased uterine contractions due to elevated estradiol level and probably some other. Association between IVF and ectopic pregnancy is still controversial and it needs further investigation. HP is a potentially life-threatening situation and should be suspected more often, as patient's first symptom is often a hemorrhagic shock [3].

Following the first FET in 1983, the technique has become an important feature of ART, resulting in high pregnancy rates, especially when transferring blastocysts [4,5]. The incidence of ectopic pregnancy following the transfer of thawed blastocysts is lower than with fresh Embryo Transfer (ET), especially if the procedure is performed in the natural cycle [6-8]. In literature, there are no reports of HP following FET of blastocysts.

Here we report a case of a HP following the FET of two blastocysts, which resulted in tubal rupture, hemorrhagic shock and emergency surgery at 7 weeks of pregnancy, but subsequently proceeded uneventfully until full term and the birth of a healthy girl.

## Case Report

A 35-year-old nulliparous woman, 7-weeks pregnant after the FET of two blastocysts, with a five-year history of infertility due to

the male factor (severe oligoasthenozoospermia), was admitted to the emergency room because of hemorrhagic shock. A week before, at the regular exam, an ultrasound revealed one gestational sac. The patient's medical history indicated she had a laparoscopic cystectomy of right paraovarian cyst five years ago, but otherwise was healthy. She had two unsuccessful IVF attempts, the second one in a previous cycle. Ovarian stimulation was accomplished using clomiphene citrate 100 mg/d (Klomifen, Belupo, Koprivnica, Croatia) from days 3-7 of the cycle, followed by human menopausal gonadotropin (Menopur, Ferring Pharmaceuticals A/S, Ferring Pharmaceuticals Inc, Parsippany, NJ 07054, USA) 150 IU/d from days 7-10 of the cycle. Recombinant hCG 250 µg (Ovitrelle; Merck Serono, Feltham, Middlesex, TW14 8NX, UK), was used to induce final follicular maturation, when one follicle of >20 mm was observed by vaginal ultrasound. Transvaginal oocyte retrieval was performed and seven oocytes were collected. Six oocytes were fertilized using the IVF. The media used were SAGE In Vitro Fertilization medium, SAGE In Vitro Fertilization cleavage medium, and SAGE Blastocyst medium (Sage Biopharma, South San Francisco, CA 94080, USA). On day 5 from the oocyte retrieval three blastocysts were vitrified (Kitazato vitrification media, Kitazato BioPharma Co., Ltd., Fuji, Shizuoka, 416-0907 Japan), and two transferred using Sydney IVF embryo transfer set (Cook Ireland, National Technology Park, Limerick, IRELAND), but the ET did not result in pregnancy.

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In a following cycle an ovulation was confirmed using a home ovulation test, and 5 days later, on cycle day 17, two blastocysts were thawed (Kitazato thawing media, Kitazato BioPharma Co., Ltd.), and FET was performed. Serum  $\beta$ HCG level 11 days after FET was 150 IU/l and 600 IU/l two days later. The TVU performed 21 day after the FET showed an intrauterine pregnancy with a cardiac activity and a Crown-Rump Length (CRL) of 1.5 mm, and raised no suspicion on HP.

At admission, the patient presented with an acute abdominal pain, dyspnea, hypotension (90/60mmHg), and weak pulse rate of 115 beats per minute. She reported no vaginal bleeding. Laboratory tests demonstrated a serum hemoglobin concentration of  $108 \times 10^{12}/l$ , hematocrit 0.30, and  $\beta$ HCG level of 55641 IU/l. On the TVU, the abdomen was filled with free fluid; the right adnexal mass was visible, together with an intact intrauterine gestation. A laparotomy was performed under general anesthesia, and two liters of blood and clots were found in the abdomen, following the rupture of the right tube. A right salpingectomy and blood removal were performed, followed by an abdominal lavage. The gravid uterus, left tube and both ovaries appeared intact. The patient received 8 units of blood during and after the surgery.

Postoperative recovery was uneventful; the patient was discharged on the sixth postoperative day and followed-up regularly. Histopathology of the right tube confirmed a diagnosis of ectopic pregnancy. The intrauterine pregnancy progressed uneventfully. At 41 weeks of gestation the patient spontaneously delivered a healthy female infant weighing 3400 grams, with a maximal Apgar score.

## Discussion

FET has a high success rate, especially if blastocysts are transferred, as the blastocyst stage of development appears to be optimal for the freezing and thawing procedures [5].

Although the first live birth after FET was reported back in 1984, the reports of HP following FET are very scarce. In 1999, a HP following FET of two embryos was reported [9], where ectopic pregnancy was abdominal, but no reports of HP following FET of blastocysts could be found. The incidence of ectopic pregnancy following the transfer of thawed blastocysts in natural cycle should be low; however, the ectopic pregnancy rate is higher when two blastocysts are transferred [10], which may explain this HP.

A preoperative diagnosis of HP is still a diagnostic challenge [11]. It has been reported that 45% of women with HP are asymptomatic, and that TVU has 93.3% sensitivity in making the correct diagnosis of HP compared with transabdominal ultrasound [12]. In our patient, who had no symptoms of ectopic pregnancy before the tubal rupture, an ultrasound at six weeks of pregnancy did not raise any suspicion of HP.

The management of HP is preferably done by laparoscopy [13], but in our patient, who was critically ill, this was not possible. There are few reports in the literature when a patient with HP presented with a hemorrhagic shock [14,15], so the management of such patients should be decided depending on the circumstances. Surgical therapy involves both surgical and anesthetic risks for the mother and the embryo, but children born from HP have the same perinatal outcome as children born after intrauterine-only IVF pregnancy, which was confirmed in our patient. However, HP's are more likely to end in abortions [16].

In the light of new findings in the literature, stating FET is even more successful in terms of pregnancy than the fresh cycle [17,18], the clinicians must be aware of the possibility of HP following FET of two blastocysts, and actively looking for it.

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