

# Heterotopic Pregnancy after In Vitro Fertilization and Embryo Transfer: A Case Report

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## SUMMARY

**Introduction** Heterotopic pregnancy is a life-threatening complication of pregnancy defined as coexistent intrauterine and ectopic gestation. Its diagnosis is frequently overlooked and delayed.

**Case Outline** A 28-year-old woman experienced acute abdominal pain in pregnancy achieved by in vitro fertilization. Since all previous checkups indicated a normal course of pregnancy, the ectopic pregnancy was not suspected on admission. However, due to persistent hypotension, this diagnosis was also considered. Transvaginal ultrasound performed by an experienced obstetrician revealed an adnexal mass highly indicative of ectopic pregnancy. No fetal heart beats were visualized and the diagnosis of a missed abortion was made. A prompt laparotomy revealed a ruptured right ampullary pregnancy, and salpingectomy was performed.

**Conclusion** Although rare, heterotopic pregnancy should be considered in the differential diagnosis of abdominal pain in pregnancy. Every physician treating women of reproductive age should bear in mind the possibility of heterotopic pregnancy not only in patients with predisposing risk factors but also in those without them.

**Keywords:** heterotopic pregnancy; abdominal pain; intraabdominal hemorrhage

## INTRODUCTION

Heterotopic pregnancy is a condition defined as coexistent intrauterine and ectopic gestations, with up to 98% of ectopic gestations being located in the fallopian tube [1]. However, cervical, ovarian, cornual and abdominal heterotopic pregnancies have been reported [2]. There is also a record of extremely rare multifetal heterotopic pregnancies [2].

The first heterotopic pregnancy was described by Duverney in 1708, in an autopsy finding [3]. In 1948, DeVoe and Pratt estimated the incidence of heterotopic pregnancy to be 1 in 30000, which was actually only a theoretical calculation derived from the incidences of ectopic pregnancies and dizygotic twinning [3]. More recent papers suggest a remarkable increase of the incidence due to several factors; general increase in risk factors for ectopic pregnancy (increasing incidence of pelvic inflammatory disease, endometriosis, tubal surgery, intrauterine device usage) and, most importantly, increasing use of ovulation induction and assisted reproductive technology (ART) [2, 4].

The true incidence in the general population today seems to be 1 in 7000 pregnancies [2]. The increasing use of ART has transformed the phenomenon of heterotopic pregnancy from being rare to relatively common. This is not unexpected, because both multiple and ectopic pregnancies (the two prerequisites for this condition) are more common in assisted conception. The increased risk of multiple pregnancies with ovulation induction and

in vitro fertilization (IVF) increases the risk of both ectopic and heterotopic pregnancies, due to multiple ovulations or multiple embryo transfers [5]. With assisted reproduction, the incidence is as high as 1 in 100 [2].

This condition represents a life-threatening complication of pregnancy. Patients usually complain of a variety of nonspecific symptoms. The diagnosis of heterotopic pregnancy is frequently overlooked and delayed, as it is typically made at surgery performed due to ectopic pregnancy [2, 3].

## CASE REPORT

A 28-year-old nullipara in the first trimester of pregnancy was referred by a gynecologist to the emergency surgical department. She had suffered abdominal pain for 7 hours, and had a history of nausea, vomiting, hypotension and urinary frequency. The patient had conceived after IVF and transfer of two embryos conducted at a different medical centre. All subsequent pregnancy checkups indicated a normal course of pregnancy. Her obstetrical history was significant for the previous ectopic pregnancy and left salpingectomy, with a 4-year secondary infertility. On examination her heart rate was 120 beats per minute, blood pressure was 80/40 mm Hg, and temperature 36.4°C. Physical examination revealed a nondistended, soft abdomen that was tender to palpation in the right lower quadrant. Abdominal ultrasound revealed normal upper abdominal organs and a viable intrauterine pregnancy without any free

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fluid. Laboratory studies showed a hemoglobin value of 87 g/l and a hematocrit level of 26%. The vital signs improved after fluid resuscitation and the X-ray scan was indicated for the bowel evaluation, which the patient refused.

She was further referred to the Gynecology Department, where she was admitted for observation. The patient looked pale, with blood pressure of 80/60 mmHg, and the heart rate of 96 beats per minute. The patient's abdomen was nondistended, with tenderness in both lower quadrants. There were no signs of peritoneal irritation. Pelvic examination revealed a closed cervix, no bleeding or vaginal discharge, and a soft enlarged uterus. No adnexal masses were noticed. A transabdominal scan showed a live embryo in the uterine cavity with a crown rump length of 33 mm, which corresponded to a gestational age of 9+3 weeks, without free fluid in the peritoneal cavity.

Two intravenous lines were established and the patient was resuscitated with intravenous fluids, human albumin and blood transfusion, which resulted in improvement of blood pressure. Repeated evaluation 2 hours later showed an increasingly tender abdomen, along with persistent hypotension. The hemoglobin concentration dropped to 77 g/l and the hematocrit level was 23.2%. Her heart rate was 120 beats per minute and blood pressure was 70/40 mm Hg. Due to hypotension and evident hemorrhagic shock, the diagnosis of an ectopic pregnancy was considered. Transvaginal ultrasound performed by a senior obstetrician revealed a mass adjacent to the right ovary of 20×25 mm, highly indicative of an ectopic pregnancy. No fetal heart beats were visualized and the diagnosis of a missed abortion was made. Within the pelvis, accumulation of echogenic free fluid thought to represent hemorrhage was seen. Provisional diagnosis of a heterotopic pregnancy with a ruptured right ectopic gestation was suggested in view of the clinical history, moderate amount of free intraperitoneal fluid and an intrauterine gestation.

A prompt laparotomy was performed via a low midline incision. It revealed a hemoperitoneum of one liter and a ruptured right ampullary pregnancy, with an actively bleeding site. The uterus size corresponded to a gestational age, both ovaries were normal, and the left tube was absent. A right salpingectomy and a thorough lavage of the abdominal cavity were performed. The intrauterine pregnancy was evacuated by dilation and curettage. Two units of blood were transfused during the procedure.

She was further transfused with three units of packed red blood cells and four units of fresh frozen plasma. The patient was discharged on the seventh postoperative day after an uneventful recovery. The presence of both the intrauterine and the tubal pregnancy was confirmed by histopathological examinations.

## DISCUSSION

Since the 1990s, the number of published cases of heterotopic pregnancy has increased considerably [5]. At the beginning of IVF, the major interest focused on pregnancy rates. However, over the last decade, the rate of

complications following multiple embryo transfer emerged as one of the major issues. A correlation between the number of embryos transferred and the chance of heterotopic pregnancy has been documented by various authors [3]. The objective of the recent tendency of reduction in the number of transferred embryos to only one or two is to minimize multiple pregnancy risk and the associated complications. Heterotopic pregnancies and resulting problems presented in our report are further reasons to encourage transfer of only one embryo in as many patients as possible.

Heterotopic pregnancy can have various presentations, most of which occur in the first trimester, like in our patient. [2]. It should be considered more likely after ART, with persistent or rising  $\beta$ -HCG levels after dilatation and curettage for an abortion, when more than one corpus luteum is present in a natural conception, and when vaginal bleeding is absent in the presence of signs and symptoms of ectopic gestation [3]. A heterotopic gestation can also present as hematometra and lower quadrant pain in early pregnancy.

The diagnosis of heterotopic pregnancy can be challenging. It is difficult and requires a high index of suspicion since it is rare and the presence of intrauterine pregnancy often impedes the diagnosis and early intervention for the ectopic pregnancy. Clinical symptoms are not generally helpful for diagnosis, which is often delayed by attributing symptoms such as pain and bleeding to complication of the coexisting intrauterine pregnancy. Physical examination usually reveals abdominal tenderness, and occasionally an adnexal mass. The typical diagnostic tools of pelvic ultrasound and measurement of serial quantitative  $\beta$ -HCG levels can be misleading, as the intrauterine pregnancy will cause the  $\beta$ -HCG to rise as expected and will be visualized by ultrasound clearly [1, 6]. Especially at early gestational age, it is not easy to make an accurate diagnosis using ultrasonography [1]. Often, it fails to show an ectopic pregnancy or is misinterpreted because of the awareness of an existing intrauterine pregnancy.

Our patient, with the risk factors for heterotopic pregnancy, namely, tubal disease and a preceding ectopic pregnancy, had undergone assisted conception with multiple embryo transfer. There were several diagnostic difficulties in our case that led to the delay in the diagnosis of ectopic component. First, the initial transabdominal ultrasound pointed to a viable intrauterine pregnancy, and thus ectopic pregnancy was not suspected. Second, initial scan failed to visualize adnexal mass as a sign of tubal pregnancy. Third, the presence of free fluid had not been noticed. Instead of using a high-resolution ultrasound, transabdominal ultrasound was initially used, the diagnosis was missed, and the patient developed intraperitoneal hemorrhage. The careful reexamination of the adnexa by an experienced sonographer demonstrated the ectopic pregnancy and the presence of fluid within the pelvis, which guided us to the right diagnosis.

The most important diagnostic method for heterotopic pregnancy is the high-resolution transvaginal sonography. Its use by an experienced ultrasonographer has been

shown to increase the percentage of correct diagnosis, as presented in our case [3]. Ultrasound can be diagnostic if fetal cardiac activity is located at two different implantation sites, but the presence of extrauterine cardiac activity is very uncommon [3]. As pointed out by various authors, detailed ultrasound studies via the vaginal route, should be performed in all patients in ART programs [2, 6]. An examination of both adnexal regions should be standard even in patients with an intrauterine pregnancy and without risk factors for heterotopic pregnancy. The sonographer should methodically examine the rest of the pelvis to exclude the possibility of a coexisting ectopic pregnancy. Presence of any free fluid within the pelvis should also prompt careful examination of the entire pelvis [3]. The routine use of early ultrasound scan after ART will lead to early diagnosis of most heterotopic and ectopic pregnancies. The patient's risk factors for heterotopic pregnancy should also be considered. These include risk factors for both ectopic and heterotopic pregnancies. Women with previous ectopic pregnancy, tubal surgery or previous pelvic inflammatory disease may be at a higher risk and should be scanned at an early gestation to confirm the location of the pregnancy. In high-risk cases, routine scanning for ectopic or heterotopic pregnancies is recommended 4 to 6 weeks after the embryo transfer [6].

The possibility of heterotopic pregnancy should be entertained whenever a pregnant woman presents with abdominal pain and signs of peritoneal irritation. It was said that an intrauterine pregnancy would rule out an ectopic pregnancy [2]. The presented case is good evidence that this is no longer true. One should be made aware that the existence of an intrauterine gestation does not preclude the risk of nidation of other fetuses in ectopic sites. This diagnosis should always be considered in the differential diagnosis in any pregnant patient with lateralized abdominal pain or an adnexal mass with or without free fluid in the pouch of Douglas. Sometimes the presence of a hemorrhagic corpus luteum can confuse and delay the diagnosis of a heterotopic pregnancy. A hypoechoic adnexal structure that is in fact an early ectopic pregnancy can be misidentified as a corpus luteal cyst. The differential diagnosis also includes ovarian hyperstimulation syndrome (OHSS) [6]. The presence of free fluid in the pelvis may be erroneously attributed to OHSS. Visualization of the ectopic coconceptus is more difficult in such cases, and the normal ultrasound indices disappear: stimulated ovaries are much larger, hurt as the probe passes, and can mask the ectopic implantation, peritoneal effusion is frequent, and the adnexa in ART patients might be pathologic. Other surgical conditions of acute abdomen can also simulate heterotopic gestation clinically. Thus, although rare, heterotopic pregnancy should be considered in the differential diagnosis of an acute abdomen.

The majority of heterotopic pregnancies are diagnosed late, usually after rupture [2]. The patients therefore present late, often collapsed and exsanguinated. Thus, women with heterotopic pregnancy are at significantly greater risk of experiencing hypovolemic shock and requirement for blood transfusion than those with ectopic pregnancy [7].

The treatment of heterotopic pregnancy is full of challenges due to the desire to preserve the normal pregnancy. It includes surgery, medical treatment, and expectant management, and its main aim is to terminate the extrauterine pregnancy, to be as minimally invasive as possible, and to preserve the intrauterine pregnancy [2].

When the diagnosis is made before the rupture of the tube, a nonsurgical treatment can be adopted. It involves sonographically guided injection of potassium chloride or hyperosmolar glucose [2]. Since the risks of continued growth and rupture still exist with such nonsurgical management, weekly follow-up, and close monitoring of clinical symptoms are essential. Monitoring serum levels of  $\beta$ -HCG is pointless in such circumstances, as they are often in the normal range due to the hormone secreted by the intrauterine pregnancy.

Operative management is still a mainstay. Because of high incidence of rupture, the current standard of care is still salpingectomy performed either by laparotomy or by laparoscopy [2]. Laparoscopy is the gold standard of treatment in selected cases. In unstable patients, laparotomy and salpingectomy is probably the safest option for the patient [2]. Surgical treatment is most appropriate if preservation of the intrauterine pregnancy is to be achieved. It is important that the uterus is disturbed as little as possible during the course of surgery and instrumental manipulation of the uterus should be avoided [3].

In the case reported here, an urgent laparotomy was performed because of the hemodynamic instability of the patient and the obvious need to get immediate control of the bleeding site. The ultimate outcome was excellent, but if the diagnosis had been considered earlier, a laparoscopic surgery might have been performed. The outcome of the intrauterine pregnancy was unfavorable possibly due to severe hypotension caused by the rupture of ectopic pregnancy, which led to intrauterine fetal demise. Since it is known that hemorrhagic shock significantly affects the intrauterine gestation, it is clear that early surgical intervention is paramount.

Delay in the condition diagnosis and failure to act quickly jeopardize both maternal well-being and survival of the intrauterine fetus. With early diagnosis and skillful treatment, the prognosis for intrauterine pregnancy is good, as in a study showing 75% of patients delivering full term, 16% preterm, and only 9% experiencing stillbirth or spontaneous abortion after laparotomy [8]. The overall survival rate of the intrauterine pregnancy is satisfactory, ranging from 65% to 92% [1]. However, with the figure of just under 1%, the maternal mortality rate of the condition is significantly greater than the death rate of 0.3% per 1,000 estimated ectopic pregnancies [1].

In conclusion, every physician treating women of reproductive age should be aware of the possibility of heterotopic pregnancy not only in patients with predisposing risk factors but also in those without them. A high index of suspicion, a diligent ultrasound examination of the adnexa and early involvement of a senior obstetrician can minimize maternal and fetal morbidity and mortality, resulting in a successful outcome for the intrauterine fetus.

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## Хетеротопична трудноћа након фертилизације *in vitro* и трансфера ембриона: приказ болесника

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### КРАТАК САДРЖАЈ

**Увод** Хетеротопична трудноћа је компликација опасна по живот труднице, а подразумева заједничко постојање интраутерине и ектопичне гестације. Њена дијагноза се често превиди и касно постави.

**Приказ болесника** Приказујемо 28-годишњу жену с акутним болом у трбуху током трудноће настале фертилизацијом *in vitro*. Пошто су сви претходни прегледи указивали на нормалан ток трудноће, при пријему се није посумњало на хетеротопичну трудноћу. Међутим, због упорне хипотензије, размотрено је и ово стање. Трансвагиналним ултразвучним прегледом који је обавио искусни акушер откривена је аднексална маса због које се посумњало на ектопичну

трудноћу. С обзиром на то да није било срчане радње плода, постављена је дијагноза изосталог побачаја. Хитна лапаротомија је показала руптурирану ампуларну трудноћу десно и урађена је салпингектомија.

**Закључак** Према је ретка, хетеротопичну трудноћу треба размотрити у диференцијалној дијагностици абдоменског бола у трудноћи. Сваки лекар који лечи жене у репродуктивном периоду мора имати на уму могућност хетеротопичне трудноће, не само код жена код којих се уочи да постоје фактори ризика, већ и код оних без њих.

**Кључне речи:** хетеротопична трудноћа; бол у абдомену; интраабдоминално крварење

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