

HETEROTOPIC TRIPLET PREGNANCY COMPLICATED WITH OVARIAN HYPERSTIMULATION SYNDROME FOLLOWING *IN VITRO* FERTILIZATION

Vlatka Tomić¹, Jozo Tomić¹, Krunoslav Kuna¹ and Đurđa Žigmundovac-Klaić²

¹Department of Human Reproduction, University Department of Gynecology and Obstetrics, Sestre milosrdnice University Hospital Center; ²Primary Gynecological Practice, Zagreb Centar Health Center, Zagreb, Croatia

SUMMARY – Heterotopic pregnancy is a rare event that occurs in less than 1% of pregnancies following *in vitro* fertilization and embryo transfer, especially when complicated with ovarian hyperstimulation syndrome. We report a case of a 31-year-old woman in the 6th gestational week of pregnancy achieved after *in vitro* fertilization, who was complaining of acute lower abdominal pain and distension, breathing difficulties and vaginal spotting. Transvaginal ultrasound examination and laboratory tests confirmed the ovarian hyperstimulation syndrome in the presence of two viable gestational sacs. The patient's condition worsened five days later with sudden onset of sharp abdominal pain, nausea and vomiting, along with impaired laboratory test values. Laparoscopy was attempted, but enlarged ovaries and adhesions prevented further procedure, which was then converted to mini-laparotomy. Operative removal of the right tubal pregnancy resulted in uncomplicated course of the intrauterine twin pregnancy and delivery of two healthy neonates by cesarean section at 37 weeks of gestation. Clinicians need to be aware of this rare complication where ovarian hyperstimulation syndrome coexists with heterotopic pregnancy after *in vitro* fertilization and embryo transfer procedure. Enlarged ovaries may mask accurate ultrasound diagnosis, but timely surgical intervention can prevent fatal consequences and result in normal course and outcome of intrauterine pregnancy.

Key words: *Heterotopic pregnancy; Ovarian hyperstimulation syndrome; In vitro fertilization*

Introduction

The ovarian hyperstimulation syndrome (OHSS) and heterotopic pregnancy are complications that may coexist after *in vitro* fertilization (IVF) and embryo transfer (ET). Stimulated cycle resulting in subsequent pregnancy is more likely to be accompanied by OHSS, particularly if multiple pregnancies occur with higher human chorionic gonadotropin (hCG) levels than singleton pregnancy¹. The incidence of se-

vere OHSS after ovarian stimulation with gonadotropins has been estimated to 0.2%-1%². Development of simultaneous ectopic and eutopic gestation occurs in less than 1% of pregnancies following IVF/ET³. Triplet heterotopic pregnancies after IVF are very rare, and when coexisting with OHSS, they make a unique and potentially life-threatening condition.

Case Report

A 31-year-old woman with primary infertility caused by tubal occlusions presented to our Department for second IVF attempt. Her hormonal status as well as her husband's semen analysis was within the normal physiological range.

Correspondence to: *Vlatka Tomić, MD*, University Hospital Center, Department of Human Reproduction, University Department of Gynecology and Obstetrics, Vinogradska c. 29, HR-10000, Zagreb, Croatia
E-mail: tomic.vlatka@gmail.com

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A short protocol of ovarian stimulation was initiated with gonadotropin releasing hormone (GnRH) and recombinant follicle-stimulating hormone (rFSH; Gonol F, Merck Serono S.A., Geneva, Switzerland). Human chorionic gonadotropin 250 mcg (Ovitrelle, Merck Serono S.A., Geneva, Switzerland) was administered when at least two leading follicles reached a diameter of 17 mm detected on ultrasound scan.

Transvaginal oocyte retrieval was carried out 35 hours later under ultrasound guidance. Of the 10 oocytes retrieved, seven were fertilized after insemination. Serum estradiol before oocyte pick-up was 2980 pg/mL. On day 3, three embryos (two grade I and one grade II) were transcervically transferred into the uterine cavity using a soft catheter (Cook IVF, Queensland, Australia) under ultrasound supervision. In luteal support vaginal micronized progesterone (Utrogestan, Laboratories Besins International, Paris, France) was given three times daily in a total dosage of 600 mg. Serum β -hCG was 780 mIU/mL, measured 14 days after oocyte retrieval.

In the 6th gestational week, the patient presented with acute lower abdominal pain and distension, breathing difficulties and vaginal spotting. Transvaginal ultrasound examination showed viable dichorionic, diamniotic twin intrauterine pregnancy. Adnexal area was dominantly covered with massively enlarged ovaries.

The diagnosis of severe OHSS was confirmed by ultrasound measurement of both ovaries (multiple corpora lutea), right 10x10 cm, left 10x9.5 cm, ascites, bilateral pleural effusion 3x3 cm, leukocytosis, lower complete protein count and borderline liver transaminases without other derangements in laboratory tests. Conservative treatment including intravenous fluid intake, albumin 20% in doses of 100 g infused over 4 hours, thromboprophylaxis with venous support stocking and heparin in a daily dose of 5000 U s.c., and analgesics was introduced. Five days later, the patient's condition worsened, signaling sharp abdominal pain located in lower abdomen on the right side, associated with nausea and vomiting. Laboratory values showed a rise in white blood cell count ($>22,000/\text{mm}^3$) and hematocrit of 29.9% (fall by 20%). Analgesic supplements did not help and laparoscopy was performed to rule out adnexal torsion or suspected extrauterine pregnancy. The attempt at laparoscopy

failed since massively enlarged ovaries and adhesions prevented us from visualizing both tubes and the procedure was converted into mini-laparotomy. The left tube was normal, but the right tube was bulky, hemorrhagic with small rupture in its continuum and hemoperitoneum of minimal extent (150 mL). However, we found a number of clots on the surface of the right fallopian tube and in the pelvic cavity. Right salpingectomy was performed. Histopathology report confirmed ruptured right tubal pregnancy and signs of inflammation in the salpingectomy specimen.

Repeat ultrasound evaluation at 10th gestational week revealed a viable twin ongoing intrauterine pregnancy with slow regression of the leading OHSS symptoms. (Fig. 1). The patient was discharged 11 days later in good healthy condition.



Fig. 1. Scan showing viable twin intrauterine pregnancy.

The intrauterine pregnancy continued without complications until 37th gestational week, when elective cesarean section was performed, resulting in delivery of two healthy boys weighing 2450 g and 2840 g, both with Apgar score 10/10.

Discussion

Triplet heterotopic pregnancy is a rare condition and very difficult to diagnose, particularly in the presence of OHSS. Heterotopic gestation after IVF is related to tubal pathology, ovarian induction and transfer of multiple embryos that increases the risk of coexistent intra- and extrauterine pregnancy⁴.

The major risk factors for ectopic pregnancy include tubal pathology, inappropriate placement of embryo, excessive force or volume during ET and retrograde migration of the embryo⁵. A higher rate of tubal pregnancy was found among patients with known tubal pathology as the cause of infertility⁶. It is assumed that at least some embryos inserted in the uterine cavity migrate into the tube. Normally, peristaltic tubal movements would expel those embryos back to the uterus, but in the presence of intratubal adhesions or even blocks, this expulsion becomes impossible.

Early ultrasound as a useful method for diagnosis of ectopic pregnancy in heterotopic gestations is often difficult due to the presence of hyperstimulated ovaries. This was also the case in our patient. In fact, only 26.3%–41.1% of cases are diagnosed with a combination of clinical and ultrasound findings^{7,8}.

Paracentesis is another important diagnostic and therapeutic tool. If symptoms of OHSS fail to improve after conservative therapy, or get even worse due to rising hCG levels of a developing intrauterine pregnancy, early paracentesis may improve the condition and help identify the coexistent complication⁹.

If blood is noticed in the peritoneal fluid, internal bleeding should be considered¹⁰. We skipped paracentesis to perform urgent laparoscopy because clinical signs led us to suspect that internal bleeding had occurred. Treatment of heterotopic pregnancy should be as minimally invasive as possible to avoid interference with the development of normal intrauterine pregnancy. With this in mind, we tried to perform laparoscopy, but extensive adhesions and gigantic ovaries prevented further procedure. The procedure was converted into mini-laparotomy to perform right salpingectomy in the presence of OHSS, with minimal manipulation of the uterus and ovaries.

First report of successful evacuation of a ruptured interstitial pregnancy and repair of the site of rupture with coexisting intrauterine twins after IVF/ET was published in 1998 by Kasum *et al.*¹¹. Moreover, a recent review reports on laparotomy to have been performed in 60.32% of surgical cases⁸. With early ultrasound and clinical diagnosis, operative treatment will result in survival of 70% of intrauterine pregnancies^{7,8}.

Nonsurgical strategies for the treatment of extrauterine pregnancy include methotrexate, etoposide, potassium chloride and hyperosmolar glucose. Since

methotrexate and etoposide have teratogenic effects, they are best to avoid in case of heterotopic pregnancy with a viable intrauterine pregnancy¹². Potassium chloride and hyperosmolar glucose have been used successfully in ectopic pregnancies, but their usage is associated with the possibility of local infections and rupture of ectopic pregnancy¹³. They should be reserved for the situations when ectopic pregnancy is clearly visualized by ultrasound.

Coexistence of heterotopic pregnancy and OHSS after IVF is always possible and remains a diagnostic challenge. Although many of intra- and extrauterine findings are nonspecific when they stay alone, the combination of ultrasound, clinical signs and laboratory values may improve specificity in identifying ectopic pregnancy. Timely surgical intervention can save the intrauterine twin gestation, with subsequent normal pregnancy course and outcome.

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Sažetak

HETEROTOPIČNA TROPLODNA TRUDNOĆA KOMPLICIRANA SINDROMOM HIPERSTIMULACIJE JAJNIKA NAKON *IN VITRO* FERTILIZACIJE

V. Tomić, J. Tomić, K. Kuna i Đ. Žigmundovac-Klaić

Heterotopična trudnoća je rijetka i događa se u manje od 1% trudnoća nakon postupka izvantjelesne oplodnje i prijenosa zametaka, pogotovo kada je komplicirana sindromom hiperstimulacije jajnika. Prikazujemo slučaj 31-godišnje žene u 6. tjednu trudnoće postignute nakon izvantjelesne oplodnje, koja se žalila na akutnu bol u donjem desnom abdomenu, napetost, poteškoće s disanjem i vaginalnu sukrvicu. Transvaginalni ultrazvučni pregled i laboratorijski testovi su potvrdili ovarijsku hiperstimulaciju u prisutnosti dvije vijabilne gestacijske vrećice. Pacijentici se zdravstveno stanje pogoršalo pet dana kasnije s iznenadnom pojavom oštre boli, mučnine i povraćanja, zajedno s pogoršanim vrijednostima laboratorijskih testova. Pokušalo se učiniti laparoskopiju, ali su povećani ovariji i priraslice spriječili nastavak operacije te je ista konvertirana u mini-laparotomiju. Operacijsko odstranjenje desne tubarne trudnoće rezultiralo je nekomplikiranim tijekom unutar maternične blizanačke trudnoće i porodom dva zdrava novorođenčeta putem carskog reza u 37. tjednu gestacije. Kliničari moraju biti svjesni moguće rijetke komplikacije u kojoj sindrom hiperstimulacije postoji uz heterotopičnu trudnoću nakon postupka izvantjelesne oplodnje i transfera embrija. Povećani jajnici mogu omesti točnu ultrazvučnu dijagnozu, ali na vrijeme izvedena kirurška intervencija može spriječiti fatalne posljedice i rezultirati normalnim tijekom i ishodom intrauterine trudnoće.

Ključne riječi: *Heterotopična trudnoća; Sindrom hiperstimulacije jajnika; In vitro fertilizacija*