

## HETEROTOPIC PREGNANCY FOLLOWING INTRAUTERINE INSEMINATION: A CASE REPORT

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### Abstract

Heterotopic pregnancy represents the diagnosis of concomitant intrauterine and ectopic pregnancies. Its incidence has increased significantly as a result of assisted reproduction procedures. Clinical presentation may be non-specific but, if diagnosis is delayed, dramatic. We present the case of a 34-year-old patient, gravida 0, para 0, who became pregnant by intrauterine insemination following controlled ovarian stimulation, presenting for vaginal bleeding and diffuse abdominal pain at 7 weeks and 4 days. Transvaginal ultrasound revealed the intrauterine and ectopic pregnancies. Following salpingectomy, pregnancy viability was confirmed at the 12 and 22 weeks scan. In conclusion we would like to emphasize that even though this pathology is scarce, in pregnancies obtained by assisted reproduction techniques a high grade of suspicion is needed.

### Rezumat: Sarcină heterotopică după inseminarea intrauterină: caz clinic

Sarcina heterotopică reprezintă diagnosticarea concomitentă a unei sarcini intrauterine și ectopice. Datorită creșterii numărului de paciente care apelează la tehnicile de reproducere umană asistată, a crescut semnificativ și incidența sarcinilor heterotopice. Manifestările clinice sunt deseori nespecifice însă, în cazul diagnosticării tardive, consecințele pot fi dramatice.

Vă prezentăm cazul unei paciente de 34 de ani, nulipara, care se prezintă pentru durere abdominală difuză și sângerare pe cale vaginală la 7 săptămâni și 4 zile de amenoree, sarcină obținută în urma unui tratament de stimulare ovariană urmată de inseminare intrauterină. Ecografia transvaginală a relevat prezența simultană a două sarcini: intrauterină și ectopică. După practicarea salpingectomiei s-a verificat viabilitatea sarcinii intrauterine. Ulterior viabilitatea a fost confirmată și la 22 de săptămâni de sarcină.

Prezentarea de caz de față dorește să sublinieze faptul că, deși această patologie este rară, este important să păstrăm unui grad înalt de suspiciune, în special în cazul sarcinilor obținute după tehnici de reproducere umană asistată.

**Cuvinte cheie:** sarcină heterotopică, inseminare intrauterină, sterilitate.

### Background

Heterotopic pregnancy (HP), represented by the simultaneous presence of intrauterine and ectopic pregnancy is a potentially lethal condition. HP may occur either spontaneously or as a result of infertility treatments. During the past years, given the uprise in assisted reproductive procedures, the reported incidence of HP increased tremendously. Thus, it was

reported to be 1:30 000 with natural conception, 1:900 with clomiphene citrate (CC) stimulation [1] and as high as 1:100 for assisted reproduction techniques, where both gametes are manipulated [2]. Signs and symptoms of HP are non-specific and include vaginal bleeding, lower abdominal pain, palpation of an adnexal mass. Serology and ultrasound are

mandatory to establish the diagnosis. The standard treatment is surgical, salpingotomy or salpingectomy depending on the degree of damage to the Fallopian tube. The present paper is a case report of HP in a controlled ovarian stimulation cycle followed by intrauterine insemination (IUI) which presented with tubal rupture.

## **CASE PRESENTATION**

A 34-year-old patient, gravida 0, para 0, with a three-year history of infertility was referred to our center for investigations and management. Patient history did not identify elements suggestive for endometriosis, pelvic inflammatory disease or other circumstances detrimental for fertility. The clinical examination did not reveal any pathologic findings. The paraclinical workup showed a hysterosalpingogram with patent fallopian tubes, normal AFC (antral follicle count) at ultrasound and stigmata of recent ovulation (presence of corpus luteum, secretory endometrium). Male fertility investigation showed normal sperm count and morphology.

The patient underwent controlled ovarian stimulation with clomiphene citrate 25mg b.i.d. during the 3<sup>rd</sup>-7<sup>th</sup> days of menstrual cycle, followed by IUI at the time of ovulation. After the third stimulation cycle we obtained polyovulation with three ovarian follicles of 16-19 mm and pregnancy was achieved (180mIU/ml HCG at 14 days post-procedure). Ultrasound examination at 5 weeks following the last menstrual period (LMP) revealed the presence of an intrauterine gestational sac with dimensions according to amenorrhea.

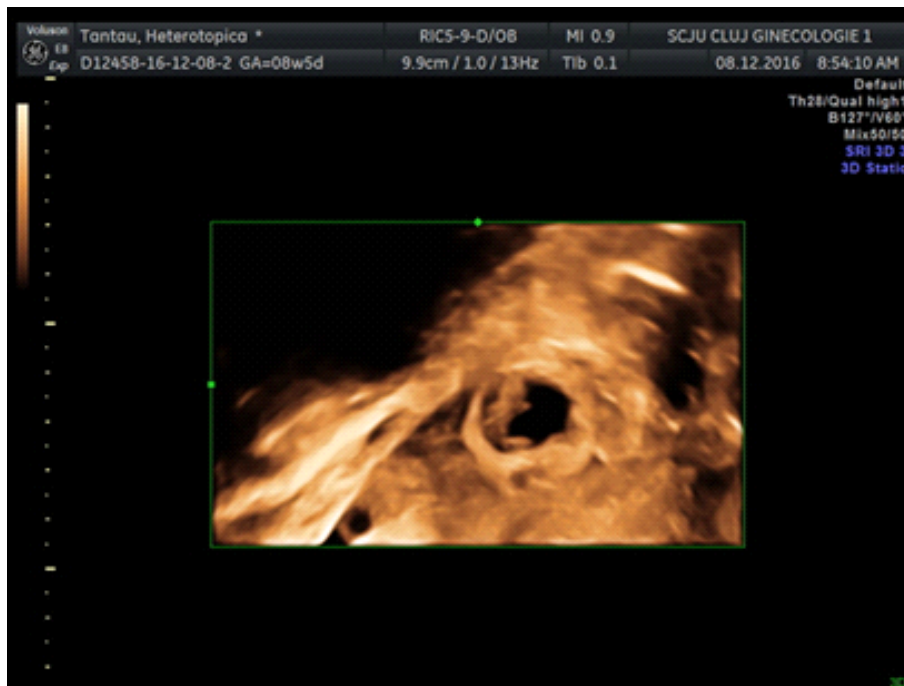
At 6 weeks and 5 days of amenorrhea the patient came to our centre for blackish metrorrhagia in moderate quantity and diffuse lower abdominal pain. HCG value at this point was 5900 mIU/ml. The patient was admitted, with parenteral antispastic treatment (Drotaverine 40 mg i.m., b.i.d.) and intravaginal progesterone (Arefam 200 mg b.i.d.). In the following 24 hours the abdominal pain intensified.

The transvaginal ultrasound examination showed an intrauterine gestational sac with a live embryo, crown rump length (CRL) corresponding to

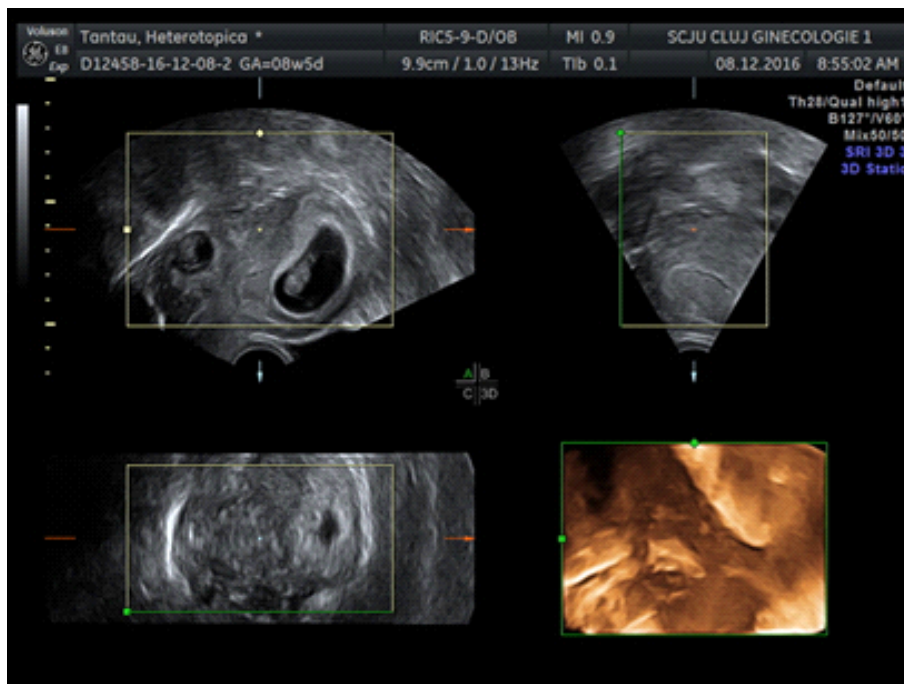
6 weeks and 7 days; in the right adnexa another gestational sac with a viable embryo was visualized, CRL corresponding to 7 weeks (*figure 1 and 2*). The left adnexa was normal and there was no free fluid in the Douglas pouch. After counseling the patient and obtaining her informed consent, diagnostic and therapeutic laparoscopy was performed under general anesthesia. Examination of the pelvis revealed scarce amount of blood in the Douglas pouch, a normally looking uterus - enlarged as corresponding to a 7 weeks gestation, a normally looking left adnexa, a normally looking right ovary bearing a corpus luteum and the right Fallopian tube distorted by the presence of the tubal ectopic pregnancy with signs tubal rupture at the point of maximum distension. Given the advanced degree of alteration of the right Fallopian tube and the tubal rupture, we considered the conservative surgical management inappropriate for the patient and performed anterograde salpingectomy. The surgical specimen was sent for pathology examination. There were no incidents during the procedure. Post-intervention ultrasound was performed to ascertain the viable intrauterine embryo. After two days of observation the patient was discharged with the recommendation of bedrest and progesterone treatment. The pathology result confirmed the diagnosis of ruptured right fallopian tube ectopic pregnancy. At the 12-week, and later 21 week follow-up the intrauterine pregnancy was viable on ultrasound.

## **Discussion**

The risk factors for HP are very similar to those for ectopic pregnancy. High genital tract infection, pelvic surgery, but especially infertility procedures are responsible for the explosive incidence of this pathology in the modern era [3] [4] [5]. The pathophysiologic pathways involved in the development of HP target two major directions: altered tubal function, altered endometrial/ myometrial function [6]. Recent research brings up the possible involvement of embryo quality among the pathophysiologic links. In this respect, IUI performed with donor sperm led to a much lower rate of ectopic pregnancy as compared to IUI performed with partner



**Figure 1.** 3D image of the intrauterine gestational sac and embryo



**Figure 2** Simultaneous presence of both ectopic and intrauterine pregnancies

sperm (often of suboptimal quality). Transfer of day 3 embryos was associated with a higher rate of ectopic pregnancy compared to blastocyst transfers [7].

Diagnosis of heterotopic pregnancy is much more difficult to ascertain than that of ectopic pregnancy. Signs and symptoms are non-specific and might be confused with other diagnosis frequently encountered in patients with infertility issues [8]. In a review of 80 cases published by Barrenetxea et al. the most common symptom for HP was low abdominal

pain (29 cases) followed by vaginal bleeding (27 cases) [9]. Differential diagnosis of these signs and symptoms are miscarriage, ectopic pregnancy [10], ovarian torsion, ruptured ovarian cyst (including luteal cyst), pelvic inflammatory disease, acute appendicitis or renal calculi [3]. When considering HP in stimulated cycles low abdominal pain can be confused with pain due to ovarian hyperstimulation [11]. The most frequent causes for the delay in HP diagnosis regarded primarily the physician (superficial examinations), but

also the patient (lack of compliance), respectively the occurrence of unusual clinical circumstances which limited the efficiency of the examination [12]. Serology has, in its turn, limited value in these cases. Variable patterns of evolution may be recorded for HCG titers produced by the ectopic trophoblast as it may increase non-exponentially as in intrauterine pregnancy, peak and then remain in a plateau or sometimes even decrease in case of non-evolutive ectopic pregnancies [13]. Ultrasound remains the elective means of diagnosis for HP. However, detection rates are much lower compared to those reported for ectopic pregnancies, firstly because of the low level of clinical suspicion [14]. The sensitivity of transvaginal ultrasound for the diagnosis of ectopic pregnancy is very high (> 95%), while for HP detection rates range was only up to 26.25% [9].

In our case, the heterotopic pregnancy was diagnosed at 7 weeks of gestation, with a 7-10 days delay compared to the detection of ectopic pregnancies post IUI or IVF (in vitro fertilization) in infertile patients. The clinical presentation of the patients was first accounted for as threatened abortion, but the evolution of symptoms mandated reevaluation of the case followed by the correct diagnosis. Surgical treatment did not have an unfavorable impact upon the intrauterine pregnancy which is viable at present (14 weeks of amenorrhea).

Conservative, systemic treatment with methotrexate is not an option for HP. Ultrasound guided injection of potassium chloride into the EP is possible, but 55% of cases need subsequent salpingectomy [15]. The most widely used procedure is salpingectomy, resulting in successful livebirth in 55-70% of cases [16]. Salpingotomy for HP is performed with much more caution compared to cases with isolated ectopic pregnancy. Although spontaneous abortion rates in patients with HP are higher (13% for HP vs. 11% intrauterine pregnancy alone), perinatal outcomes are similar [17].

Unfortunately, HP where the second pregnancy is cornual, cervical, or located in the caesarean scar have higher complication rates and raise much more complex treatment issues which require extensive obstetrician experience.

## Conclusion

Ultrasound confirmation of intrauterine pregnancy does not exclude the possibility of ectopic pregnancy. Minute imaging of the adnexa is mandatory in all first trimester pregnancies and especially in patients with risk factors for ectopic pregnancy, with the use of ovulation-inducing medications or assisted reproduction technologies. An atypical evolution of HCG values or an unusual clinical scenario advise caution. The first ultrasound evaluation post infertility treatment should be at 5 weeks, performed by an experienced sonographer. Delay in diagnosis may lead to serious adverse consequences, both for the normally implanted embryo and for the patient's life (cornual, cervical pregnancy). Counseling of patients with regard to these risks at the beginning of infertility procedures is essential.

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