



## Case Report

# Ovarian Heterotopic Pregnancy after Ovulation Induction: A Case Report

**Manuela Viviano\*, Shahzia Lambat Emery, Federico Del Vento, Manuela Undurruga Malinverno, Jasmine Abdulcadir**

Division of Gynecology, Department of Pediatrics, Gynecology and Obstetrics, Geneva University Hospitals, Geneva, Switzerland

**\*Corresponding author:** Manuela Viviano, Division of Gynecology, Department of Pediatrics, Gynecology and Obstetrics, Geneva University Hospitals, Geneva, Switzerland

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## Abstract

Heterotopic pregnancy is a rare condition defined by the concomitant presence of an intra-uterine pregnancy and one that is located elsewhere, usually in the fallopian tube. Even rarer is the ectopic component's localization in the ovary. Because of the low prevalence of this condition, its diagnosis can be challenging. Skillful treatment is required in order to avoid its evolution toward hemorrhage and maternal mortality or loss of the intra-uterine pregnancy. We present the case of a healthy 31-year-old woman, gravida-I para-0, at 5 gestational weeks of a pregnancy obtained as a result of ovulation induction using gonadotropins. The woman presented to the emergency unit with intense abdominal pain. Workup showed a right adnexal mass and a concomitant intra-uterine viable pregnancy whose gestational age corresponded to her last menstrual period. Emergency laparoscopy was performed, allowing removal of the right adnexal mass that was located in the homolateral ovary, associated with 700 ml of hemoperitoneum. Her post-operative course was uneventful; her intra-uterine pregnancy is currently ongoing and followed on a regular basis. Ovarian heterotopic pregnancy is a rare condition that necessitates a rapid diagnosis followed by immediate treatment in order to avoid life-threatening consequences.

**Keywords:** Heterotopic pregnancy; Ovarian pregnancy; Ovulation induction; Spontaneous conception; Extra-uterine pregnancy; Extra-uterine pregnancy

## Introduction

Heterotopic pregnancy (HP) is a rare entity, found in only 1/30'000 spontaneous pregnancies [1]. However, among pregnancies originated from assisted reproductive technology (ART), the incidence of HP increases to 1/3000 [1,2]. The 10-fold increase in the incidence of HP applies especially to pregnancies obtained from in-vitro fertilization and embryo transfer (FIVET) and intracytoplasmic sperm injection (ICSI) [3]. While ovulation induction followed by timed coitus or intra-uterine insemination (IUI) is associated with higher odds of multiple birth, its association with HP is less frequent accounting for about 2.1% of all HPs obtained with the use of ART [4,5]. The most common site of the extra-uterine component is the fallopian tube, which is

observed in up to 85% of HP [6-8]. A less frequent location is the ovary, accounting for 3% of all ectopic pregnancies and 2.3% of all heterotopic ones [1,9]. Embryonic structures within the ovary are usually not visualized, as progression beyond the early stages is rare [10]. While an HP should be suspected in a symptomatic patient who has undergone ovulation induction or other ARTs, the diagnosis of HP remains a challenging one. Common symptoms include abdominal pain and mild uterine bleeding in a woman with a positive pregnancy test, all of which can also be found in an otherwise normally evolving pregnancy, a miscarriage or an ectopic pregnancy [11]. Ultrasonography has limited sensitivity and  $\beta$ -hCG dosage is little to not helpful in the early diagnosis of HP [4,12]. It is usually by combining ultrasonographic and clinical findings that the preoperative diagnosis can be made, the rapidity of which is essential in preserving the woman's life and the intrauterine pregnancy. We hereby present the case of an ovarian HP after ovulation induction with gonadotropins, and we

discuss the diagnostic and therapeutic challenges associated with this rare condition.

Case Presentation

A 31-year-old woman, gravida-I para-0, presented to the gyno-obstetrical emergency unit of the Geneva University Hospitals for abdominal pain. According to her last menstrual period, she was 5 6/7 gestational weeks (GW) pregnant. The patient was known for a history of 15 months primary infertility, for which she had first consulted at our institution in March 2021. Her medical-surgical history was marked by a hysteroscopy with polypectomy two years earlier and a surgical ablation of bilateral breast fibroadenomas. She was known for a fundic uterine myoma, classified as International Federation of Gynecology and Obstetrics (FIGO) 7, measuring about 3 cm. She was underweight, with a Body Mass Index (BMI) of 16.2 kg/m<sup>2</sup>. Investigations had revealed a normal uterus and ovaries, as well as patent left and right fallopian tubes. Her husband’s semen analysis was normal. Her AMH level was 8.6 pmol/l and her antral follicular count (AFC) was 7 and 2 in the right and left ovary, respectively. Results were consistent with an ovarian reserve potentially associated with a low prognosis of assisted reproductive technology

treatments, classified as Poseidon 1b and the suggested treatment was ovulation induction followed by intra-uterine insemination [13]. She underwent her first round of ovulation induction using recombinant FSH at a dose of 62.5 mg per day on July 15th, 2021, which was administered for a total of 10 days. Ultrasonography performed after 9 days of stimulation on July 26th, 2021 showed one corpus luteum on the right ovary and a progesterone that had reached a value of 1.14 µg/l. As a spontaneous ovulation occurred during the weekend, the insemination was canceled, and the patient was advised to have unprotected intercourse. Her first dosage of beta-human Chorionic Gonadotropin (β-hCG) showed a value of 550 U/l on August 9th, 2021, followed by a second dosage after 48 hours, showing a β-hCG value of 1249 U/l. On August the 25th, she arrived at the emergency unit by ambulance complaining of abdominal pain, which had suddenly begun two hours earlier at home and was described as continuous, located in the lower abdomen with an intensity of 9/10 on the visual analogue scale (VAS). She also reported nausea and vomiting in the past 3 days without diarrhea nor fever. She had not yet had a gynecological ultrasound since the beginning of her pregnancy and her first ultrasound was scheduled in two days. The timeline of the patient’s case is resumed in Figure 1.

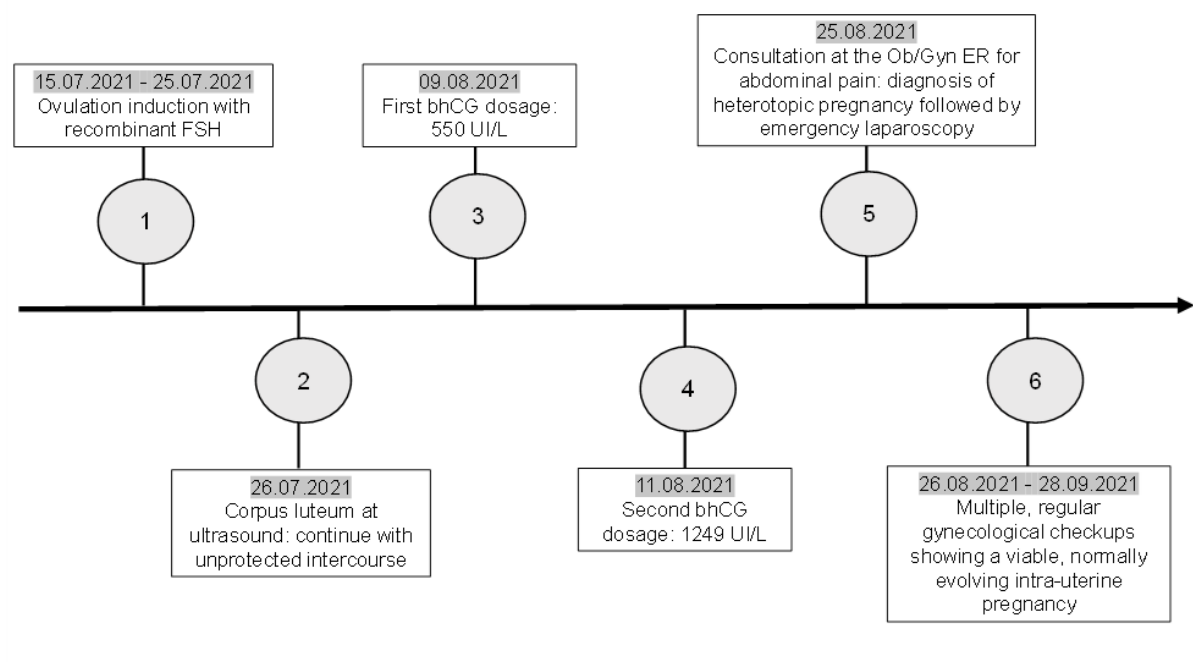


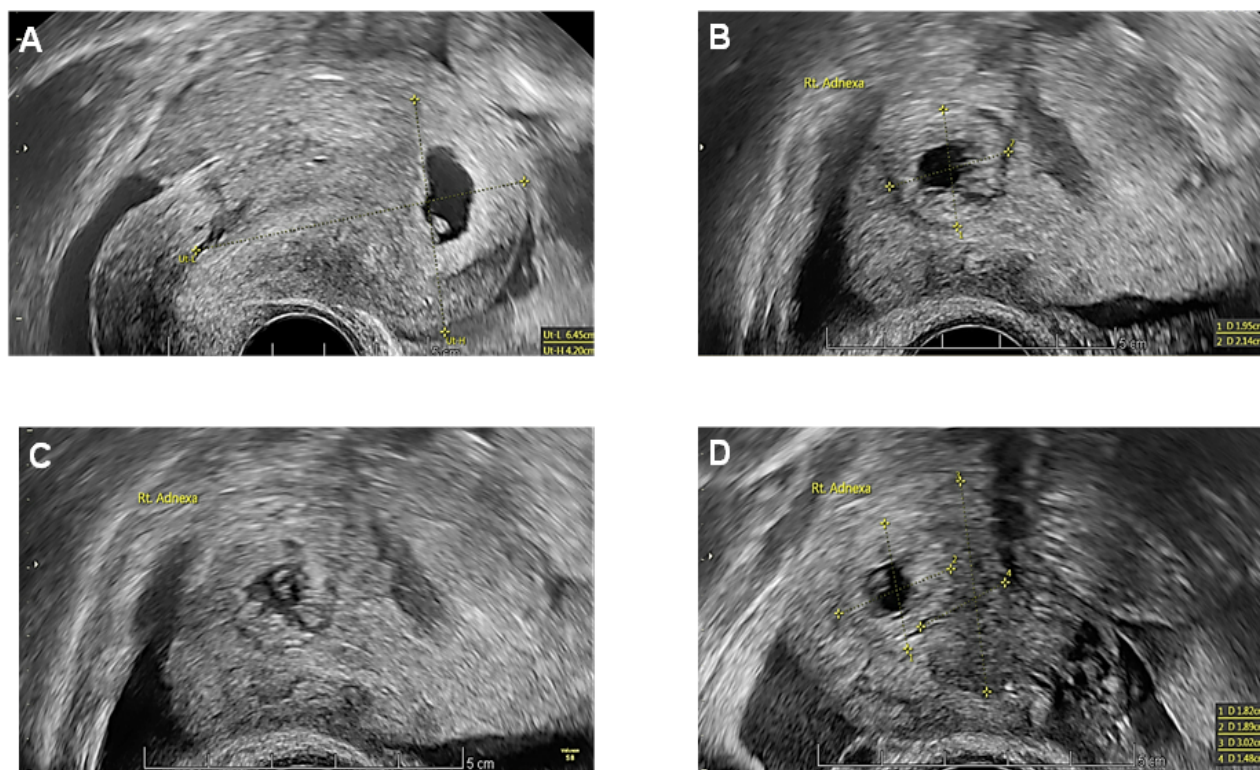
Figure 1: Timeline of the patient’s case.

The woman's abdominal examination revealed bilateral lower quadrant tenderness that was more intense in the right inferior abdominal quadrant. At pelvic examination, she had a closed cervix with physiological discharge. Transvaginal ultrasound showed an anteverted uterus with a gestational sac localized in the endometrium. Within the gestational sac, a yolk sac and an embryo were visualized, the latter of which had a crown-rump length (CRL) of 6 mm and a heartbeat. There was free fluid in the Douglas pouch that reached the uterine fundus and was estimated to be about 250 ml. The right adnexa presented a round hyper-echoic mass measuring 21 mm in diameter with a hypo-echoic center, in which a yolk sac and an embryo with heartbeat were visualized. The left adnexa appeared normal. Ultrasounds images are shown in Figure 2. Given the free fluid in the abdomen, the presence of an adnexal mass concomitant to an intra-uterine pregnancy, and her acute abdominal pain, an emergency laparoscopy was organized.

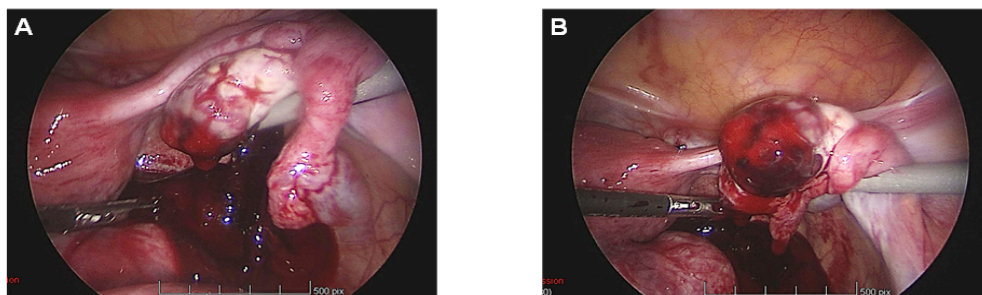
The patient's hemoglobin upon her arrival at the emergency unit was 112 g/l, the hematocrit was 32%. While her vital

parameters were initially stable, her blood pressure began to slightly drop before entering the operating room.

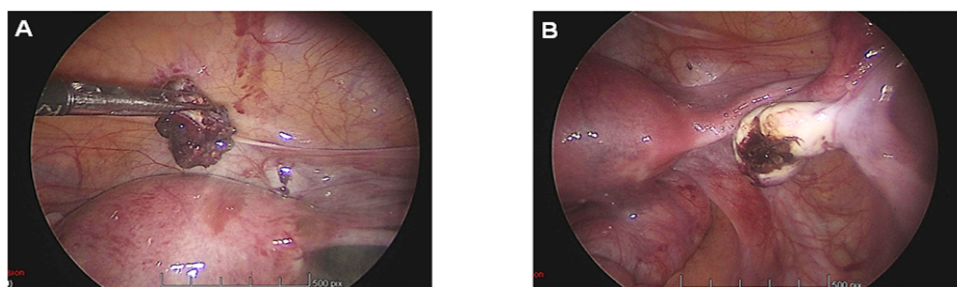
The patient underwent an emergency diagnostic and operative laparoscopy during which we were able to identify that the adnexal mass was in fact located in the right ovary. The mass was removed with the use of a bipolar diatermocoagulator. Two corpus luteum were visualized, one in the right and one in the left ovary, both of which were left intact. The right and left fallopian tubes appeared normal. Up to 700 ml of hemoperitoneum were removed from the abdominal cavity. Laparoscopic images are shown in Figure 3 and Figure 4. Histological analysis of the right ovarian mass identified the presence of chorionic villi. The post-operative period was uneventful, and the woman was dismissed from hospital the day after her surgery. The patient was prescribed intra-vaginal progesterone at a dose of 200 mg per day as of the first post-operative day. Her pregnancy proceeded without any further complications, and she gave birth to a healthy infant at 39 2/7 gestational weeks.



**Figure 2:** Ultrasound assessment of (A) intra-uterine and (B-C-D) extra-uterine pregnancy.



**Figure 3:** Laparoscopic assessment showing ovarian pregnancy with free fluid in the pelvis (A and B).



**Figure 4:** (A) Removal of the ovarian pregnancy during laparoscopy and (B) right ovary after removal of the extra-uterine pregnancy.

## Discussion

HP is a life-threatening condition for both the woman and her intrauterine pregnancy. The ectopic component's growth can rapidly lead to rupture of the tissues surrounding it resulting in hemorrhage, hypovolemic shock, maternal mortality, and fetal loss [14]. While HP is rare in the general population, ectopic ovarian pregnancy is even rarer, with an estimated incidence of 1/25'000-40'000 pregnancies [15]. As both these conditions are unusual, their early detection is challenging but also fundamental in order to avoid their life-threatening consequences. Risk factors which should raise suspicion for HP include pregnancy obtained through ARTs, endometriosis, polycystic ovarian morphology, and pelvic adhesions [16-18]. It would be intuitive to believe that, in order to prevent the ectopic pregnancy's progression beyond its early stages, ultrasonographic scans should be scheduled early enough in pregnancy, especially for patients presenting common risk factors for HP [19]. However, one of the limits of the sonographic detection of HP is its low sensitivity, with a value of 0.56 according to Xu Y et al [12]. In addition, cases of HP identified only at 13 and 17 GW have been reported in the medical literature, showing how poorly classic diagnostic features may perform in this rare condition [20,21]. In their case series, Jeon JH et al found that, despite early ultrasonography performed in patients who had

undergone FIVET and presented a HP, only 16% of asymptomatic women were correctly diagnosed with HP (4). Moreover, patients who have undergone ovulation induction may present with a concomitant Ovarian Hyper-stimulation Syndrome (OHSS), where the enlarged ovary may hide the ectopic pregnancy, making the diagnosis of HP even more challenging and possible only later in gestation, when the condition becomes a surgical emergency [20,22,23].

The addition of  $\beta$ -hCG dosage is only limitedly helpful in the early diagnosis of HP. An initial rapid decrease in  $\beta$ -hCG values can be misleading, as the intrauterine pregnancy may evolve in a spontaneous miscarriage while the ectopic one grows undisturbed [24]. Ibrahim et al found that a proper increase in  $\beta$ -hCG values over a period of 3 weeks, in a patient who has undergone ovulation induction and presenting with symptoms of OHSS, could falsely lead to the diagnosis of a normally evolving intra-uterine pregnancy with no associated ectopic component [20]. In our case, the patient had two  $\beta$ -hCG dosages at approximately 4 GW while being asymptomatic, which were indicative of a favorable pregnancy outcome, and indeed they were associated with a viable intra-uterine pregnancy. The diagnostic challenge of HP is therefore due to multiple factors such as the impossibility of recognizing it early enough at ultrasonography, the limited utility of  $\beta$ -hCG dosage

and the clinical manifestations that may mimic other conditions. In our patient, it was the sudden onset of symptoms, together with the ultrasonographic findings showing an adnexal mass and free fluid, as well as her history of ovulation induction that allowed early diagnosis and management of the HP. Surgical management, followed by histological analysis of the removed specimen, allows the definitive diagnosis of ovarian HP [8]. Spielberg's criteria for ovarian pregnancies, which include (I) intact fallopian tube on the affected side, (II) fetal sac occupying the ovary, (III) connection of the ovary to the uterus by the ovarian ligament and (IV) histological confirmation of ovarian tissue in the gestational sac wall, date back to 1878 and may have led to an under-diagnosis of ovarian pregnancies, as most surgical specimens do not include ovarian tissue. For this reason, they have recently been replaced by less strict criteria, such as the noninvolvement of the homolateral fallopian tube and the presence of chorionic villi within the ovarian mass, both of which were found in our case [25,26].

It is estimated that the live birth rate after surgical management of a HP, regardless of the site of the ectopic component, is between 58 and 70% [27]. Laparoscopy is the chosen access in most cases, reserving laparotomy to unstable patients [28]. While oophorectomy was the preferred surgical technique in the past and may still be used in selected cases of severe hemorrhage, resection of the ectopic pregnancy while preserving the rest of the ovary is the currently preferred technique [28-30]. According to Odejinmi F et al, out of 12 patients presenting with ovarian pregnancy and treated with laparoscopy only one of them required an oophorectomy [31]. Kasahara Y et al described a series of 4 cases of ovarian pregnancy, all of which were laparoscopically resected while preserving the rest of the ovary [28]. In our case, laparoscopy allowed removal of the ovarian pregnancy as well as of the 700 ml-hemoperitoneum with no intra- or post-operative complications and a currently normally evolving intra-uterine pregnancy. Primary prevention of heterotopic pregnancy can be achieved through appropriate ART protocols while being careful not to compromise intra-uterine pregnancy rates [32]. While Clomiphene Citrate (CC) has classically been used as the first line therapy for women with anovulatory disorders, Letrozole is starting to replace it, with higher rates of monofollicular growth compared to CC and a relative risk (RR) of multiple pregnancies of 0.495 (95%CI 0.261-0.939) [33,34]. Gonadotropins are a valid alternative for women with resistance to CC, with an improved live birth rate (RR 1.24, 95%CI 1.05-1.46) while maintaining a similar multiple pregnancy rate (RR 0.89, 95%CI 0.33-2.44) [35]. In the same Cochrane review, Weiss et al found a live birth rate of 41% and 43-60% with continued CC and FSH, respectively [35].

To overcome such issue, Scalici E et al demonstrated that the number of intermediate follicles (12-15mm) was an independent risk factor for multiple pregnancies [36]. In their prospective study,

Li S et al used low-dose gonadotropins for ovarian stimulation and selected only follicles  $\geq 14$ mm as the growing ones to reduce the multiple pregnancy rates [37]. The authors found increased ectopic pregnancy rates from 2.36% to 12.12% when IUI was preceded by a natural cycle or two growth follicles in an HMG-induced cycle, respectively. Such difference, however, was not significant when comparing natural cycles to one growth follicle ones. As the clinical pregnancy rates were similar between one- and two-follicle induction cycles, the authors concluded that one follicular growth is sufficient to obtain a satisfying pregnancy outcome while counterbalancing the risk of multiple or ectopic pregnancy [37]. A recent Cochrane review found that the rate of ectopic pregnancy following single IUI is 0.8%, while the same rate following double IUI reaches 3.2% [38]. In their analysis of 553,577 pregnancies obtained with embryo transfer, Perkins KM, et al. observed that higher FSH doses were associated with proportionally higher rates of ectopic pregnancies, the latter of which also included heterotopic gestations [39]. Moreover, the rate of ectopic pregnancies increased from 1.6% to 2.5% when one and four embryos were transferred, respectively [39]. In conclusion, certain groups of women have a higher risk of HP, with possible life-threatening consequences for their own health and for the intrauterine pregnancy. In the wide spectrum of ARTs, elective single-embryo transfer and milder stimulation protocols are effective strategies to avoid multifollicular development while maintaining acceptable live-birth rates [40-43]. Closer follow-up in the first weeks of pregnancy could be proposed to selected women. Cost-effectiveness and intention-to-treat trials may be conducted with the purpose of identifying whether it would be useful to increase gynecological visits to detect a rare, but potentially life-threatening condition.

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