European Review for Medical and Pharmacological Sciences 2024; 28: 4469-4476

Ectopic pregnancy on the uterosacral ligament post-double frozen embryo transfer in an endometriosis patient: case report and review of management and treatment options

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Abstract. – BACKGROUND: Ectopic pregnancy (EP) is a serious obstetric condition that can be life-threatening, with various risk factors contributing to its development. In particular, in vitro fertilization (IVF) techniques may lead to an increased rate EP. Additionally, also endometriosis seems to be related to this particular obstetrical condition.

CASE REPORT: We report a rare case of ectopic pregnancy on the uterosacral ligament (USL) along with a suspected coexisting tubal ectopic pregnancy following IVF. The patient is a 48-year-old woman in menopause, with a history of pelvic endometriosis, who experienced sudden abdominal pain and vomiting at eight weeks of amenorrhea after undergoing a double heterologous frozen embryo transfer. Thorough examination and pelvic ultrasound, we diagnosed a hemoperitoneum due to a suspected heterotopic EP on the left USL and contralateral tube. Due to the sudden worsening of the patient's condition, we opted for a surgical procedure. An urgent laparotomy revealed a severe hemoperitoneum caused by an EP implanted on the left USL and a malacic, bleeding contralateral tube, both of which were removed, and hemostasis was then guaranteed. The histopathologic exam confirmed the EP on the left USL and an edematous tube without product of conception (POC).

CONCLUSIONS: Comparing our case with others reported in the current literature, it appears that the etiopathogenetic mechanisms leading to this urgent obstetrical condition are various and not fully understood. Despite those circumstances, the present case highlights the importance of considering non-tubal ectopic pregnancies in the context of risk factors, including IVF techniques, endometriosis, and advanced age, in cases of abdominal pain and hemoperitoneum after a single or double embryo transfer. The treatment, which involves different professional figures, should be executed as soon as possible, with the aim of preserving the patient's life and any future desire for pregnancies.

Key Words:
Ectopic abdominal pregnancy, Endometriosis, IVF techniques, Utero-sacral ligament, Hemoperitoneum.

Introduction

Ectopic pregnancy (EP) is an obstetrical condition in which the fertilized ovum implants outside the uterine cavity, with a frequency of 2-3% of all pregnancies. Specifically, abdominal pregnancies account for around 10% of all EP[1]. This obstetrical condition has a high risk of mortality for women because, if undiagnosed, EP may result in organ rupture, hemorrhage, and hypovolemic shock, leading to a mortality rate of around 10%[2]. Nowadays, due to earlier and more accurate diagnoses, as well as easier access to medical and surgical treatment, maternal mortality from EP has notably decreased.

Among EPs, abdominal pregnancies are characterized by an implantation site involving the omentum, peritoneum of the pelvic and the abdominal cavity, the uterine surface, and abdominal organs, such as the spleen, intestine, liver, and blood vessels[3].

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There are two types of abdominal pregnancy[4]: primary abdominal pregnancy, which results from the implantation of an embryo in the abdominal cavity, and secondary abdominal pregnancy, which results from the implantation of a pregnancy into the abdominal cavity that was previously located elsewhere (e.g., ruptured tubal pregnancy).

In these cases, the diagnosis is very difficult and challenging due to the heterogeneity of symptoms, localization, and clinical evolution. Current diagnostic methods for abdominal pregnancies, as well as for all EP, rely on serum β-hCG levels in correlation with trans-vaginal ultrasound (TV -US) or trans-abdominal ultrasound (TA-US). In some cases, as for abdominal sites, magnetic pelvic resonance (MRI) can lead to a correct diagnosis[5]. β-hCG levels are fundamental to monitor and to determine a miscarriage or fetal development pattern[4]: a patient with a β-hCG level > 1,000 mIU/mL with no ultrasonography signs of intrauterine pregnancy (IUP) is highly suspicious for EP. Specifically, TV-US has been shown to be more accurate and sensitive than TA-US in diagnosing early EP[6].

The rate of ruptured ectopic pregnancies (EP) is around 15% in Western countries, with the fallopian tube being the most commonly affected site. The risk of maternal mortality is 50 times higher compared to first-trimester pregnancy termination and 10 times higher than third-trimester delivery. Other sites of EP, such as abdominal ones and uterosacral ligaments (USL), must be considered in suspected cases of non-intrauterine pregnancies.

Risk factors associated with EP are various, although about half of patients did not exhibit any of them. These include prior EP, damage to fallopian tubes, prior pelvic surgery, complications from ascending pelvic infection, prior fallopian tube surgery or pathology, infertility, smoking, age greater than 35 years old, pelvic inflammatory disease, endometriosis, variant reproductive system anatomy, pregnancy that occurs with an intrauterine device (IUD) and use of assisted reproductive technology (ART)[7].

Indeed, the incidence of EP may increase dramatically with ART, occurring in approximately 2.1-8.6% (higher than the 2-3% described before, after a spontaneous conception) of women undergoing the technique, and sites of implantation can be various. Most EPs from either IVF or spontaneous pregnancy may occur in locations other than the fallopian tubes, such as the cervix, ovary, or abdomen[8].

There are some specific risk factors for EP in assisted reproductive technology (ART), such as reduced tubal contractility due to high levels of progesterone produced by multiple corpora lutea, hypervascular ovaries after hyperstimulation, and follicular growth induction by gonadotropins. At the same time, embryo-transfer procedures may be involved in the pathogenesis, particularly deep fundic embryo transfer (ET), which implicates a large number of transferred embryos: specifically, embryos can migrate into the fallopian tubes due to the retrograde effect of uterine contractions.

Additionally, the pressure exerted by the culture medium containing the embryos may also contribute to embryo migration in the fallopian tubes, and the risk is increased with more than 80 microliters of culture medium[9].

We report a case of suspected heterotopic EP after IVF heterologous techniques and a review of the management and treatment of this obstetrical condition, with the aim of exploring a possible link with IVF, endometriosis, and the evolution of this life-threatening condition.

Case Presentation

The patient is a 48-year-old primigravida who presented to the Obstetrics and Gynecology Unit at Sandro Pertini Hospital in Rome, Italy, on November 19, 2023. She arrived at the hospital 8 weeks after undergoing a double heterologous embryo transfer (ET) and reported a 1-day history of sudden, worsening, sharp, colicky abdominal pain accompanied by nausea and non-bilious vomiting, with episodes of diarrhea. She had no vaginal bleeding, no contact with sick individuals, and no history of traumatic injuries. During the physical examination, she appeared slightly drowsy, was afebrile, and had a heart rate of 145 beats per minute. She was also hypotensive, with a blood pressure reading of 84/50 mmHg. Her abdomen exhibited severe tenderness in the left lower quadrant without rebound tenderness or guarding. On speculum examination, the cervical ostium was closed with no evidence of vaginal bleeding or discharge. She experienced severe pain during the transvaginal ultrasound (TVS) examination and in the Douglas region.

Woman's Medical History

The patient did not have any diseases such as diabetes or hypertension, nor had she undergone any previous surgical procedures. She

experienced primary infertility and had been in menopause for 4 years. She was diagnosed with pelvic endometriosis, specifically adenomyosis, and deep infiltrating endometriosis, with adhesions in the Douglas region. She presented recent pelvic ultrasound examination conducted before the start of IVF, revealing a normal endometrial cavity with no endometrial polyps or submucosal lesions, such as myomas, and no ovarian endometriomas. She had two heterologous blastocysts transferred on day 5 in a frozen cycle at an IVF center outside Italy on September 23, 2023. The pharmacological therapy she received consisted of oral estradiol 8 mg per day and vaginal progesterone 800 mg per day. Two weeks later, her beta-human chorionic gonadotropin (β-hCG) level was 982 mIU/mL, and an ultrasound check performed 4 weeks post-ET at another IVF center showed no intrauterine gestational sac (IUGS) or adnexal mass visible on the scan. The patient was asymptomatic at that time, and another ultrasound was scheduled for two weeks later. Unfortunately, on November 19, 2023, she was admitted to the emergency department with acute abdominal pain and vomiting.

Diagnosis

Following the medical history, biochemical exams were conducted along with beta-HCG values. A TV-US revealed a thickened and heterogeneous endometrial lining and a suspected retro-uterine mass (Figure 1 A-B), with blood clots and free fluid effusion observed in the pouch of Douglas and around the bowel, as well as in Morrison's pouch. The beta-HCG value was 1,890 mg/dl, and the baseline hemoglobin level was 8.5 g/L. Blood group testing and crossmatching were conducted, and two units of blood were prepared for transfusion. Due to the worsening of the patient's condition approximately 30 minutes after admission, a surgical procedure became necessary. Consequently, the patient underwent an urgent laparotomy for a suspected ectopic pregnancy.

Surgical Procedure

An urgent Pfannenstiel laparotomy revealed a severe hemoperitoneum with more than 1.5 liters of free blood in the pelvis, which was immediately aspirated, and blood clots were evacuated. The operative findings showed a normal 7-week uterus with a normal right fallopian tube, whereas the left fallopian tube was edematous and hemorrhagic, and both ovaries were normal (Figure 2A). Active bleeding was noted over the left USL, raising suspicion of products of conception (POC) (Figure 2B). The ureter was identified, and the POC was carefully dissected from the left USL, and the tissue was sutured by absorbable interrupted suture (Figure 2C). In addition, the left tube was also removed, as it appeared edematous, malacic, and hemorrhagic. Suspected ectopic pregnancies from USL and left tube were collected and processed for histological exam. Topical hemostatic agents, including oxidized regenerated cellulose and human gelatin thrombin matrix, were applied over the left USL to ensure hemostasis. The abdomen was closed with resorbable sutures. Two units of packed blood cells were transfused intraoperatively, with an estimated blood loss exceeding 2,500 mL. The patient

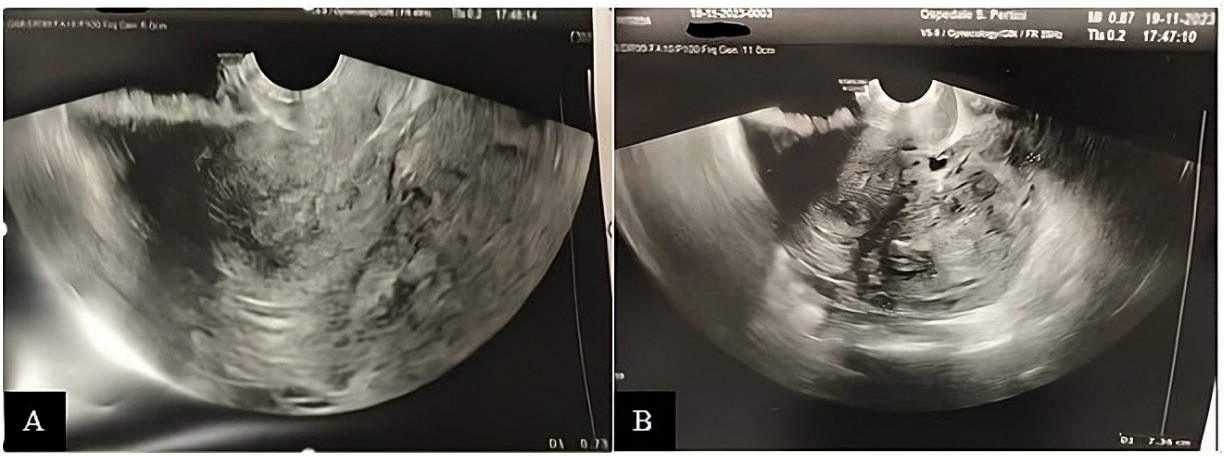

Figure 1. A, The ultrasound picture shows the patient's uterus, specifically the endometrial line of 7.3 mm, without images of the intrauterine gestational chamber. **B**, The ultrasound scan shows a "complex max" of around 7.3 cm below the uterus and the cervix, next to the utero-sacral region, deponent for suspected ectopic abdominal pregnancy and blood clots.

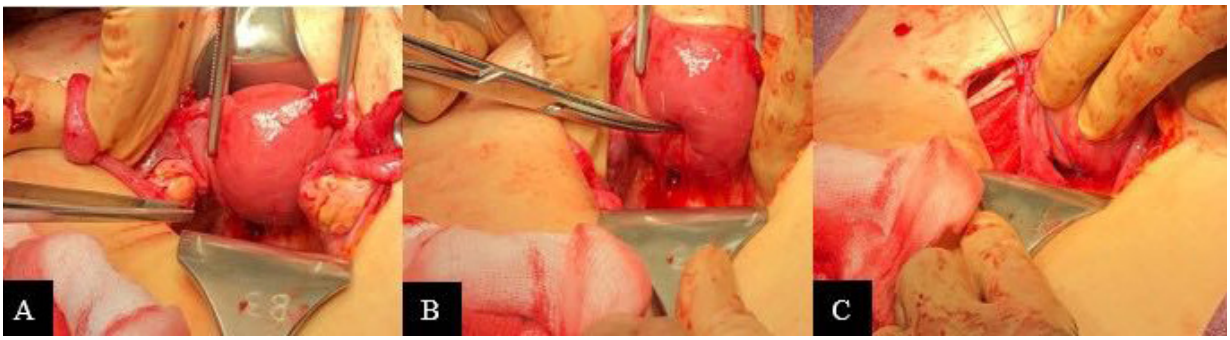

Figure 2. A, Urgent abdominal Pfannestiel laparotomy, specifically in the uterine posterior wall where the left USL ectopic pregnancy was located with a bleeding cavity close to the USL region. **B**, The suspected product of conception (POC) was then removed. **C**, The continuous solution of the cavity was sutured with detached stitches, and hemostasis was then guaranteed.

remained hemodynamically stable in the ward, with a hemoglobin level of 8.1 g/dl on postoperative day 1 and was discharged well on postoperative day 3 with a level of 8.9 g/dl. A single dose of intramuscular progesterone 100 mg was injected, and she was prescribed an oral progestogen 10 mg twice daily. Histopathological examination of the resected specimen confirmed the presence of vascularized chorionic villi consistent with POC, whereas the left fallopian tube histological exam showed only edema without POC. One month after the surgical procedure, a follow-up visit and pelvic ultrasound were performed, confirming the patient's good condition with a negative value of serum hCG hormone.

Discussion

EP is a cause of morbidity in pregnancy and is responsible for approximately 10% of pregnancy mortality, especially in the first trimester of pregnancy. Intra-abdominal hemorrhage is a catastrophic complication of EP that requires prompt treatment. Although most cases (approximately 80%) are hemodynamically stable at diagnosis, early diagnosis is crucial to avoid life-threatening events and to allow less invasive surgical procedures[10]. Currently, diagnosis has become more sensitive, including the combination of serum β-hCG measurements with sonographic features. Quantitative B-hCG levels can be performed with TV-US for early diagnosis of EP, with around 50% (49.1%) of cases diagnosed at presentation, with a sensitivity of 100% and specificity of 99.9%. Abdominal EP is a rare form of EP where the diagnosis can be challenging due to atypical presentation, and it is characterized by high potential of morbidity[11]. Although it accounts for 1% of all EPs, it has a maternal mortality rate that is eight times higher than that of tubal ectopic pregnancies[12]. Therefore, early recognition and treatment of abdominal EP are crucial, and there are three different approaches: waiting, medical, or surgical management.

Waiting Approach

There are few cases reported in current literature, such as one that illustrates an abdominal mass located in the Douglas pouch that remained *in situ* for nearly 3 years after the serum human chorionic gonadotropin levels tested negative[13]. Due to persistent defecation pain, a laparoscopic remotion of the mass was finally performed. The authors noted that while abdominal pregnancies, like tubal pregnancies, can be managed through expectant observation, it should be considered that the abdominal pregnancy mass may persist for a longer time and potentially cause symptoms requiring surgical intervention.

A single prospective randomized trial compared expectant management with the administration of a single dose of methotrexate to women with pregnancies that were either extrauterine or of uncertain location[14]. There was no significant difference between the two groups regarding the uneventful decline in serum hCG levels below the detection threshold. Due to the limited evidence available, watchful waiting cannot be considered and recommended as a therapeutic option.

Medical Treatments

Methotrexate is the only drug that can be used for the medical treatment of EP: it is a folate antagonist that interferes with the rapidly dividing cells, as the ones of the EP, and its success rate

decreases with higher initial β-hCG levels, as reported in NICE guidelines[15]. This treatment presents teratogenic effects and should only be considered in heterotopic pregnancies if the IUP is not viable or undesirable. However, it is not a routine treatment due to the high risk of failure and the potential adverse outcomes, such as hemorrhage or rupture. Other conservative medical treatments for hemodynamic stable patients include intracardiac potassium chloride or local hyperosmolar glucose injection with gestational sac aspiration, both of which, in some cases, have reported medical success[16].

Surgical and Alternative Procedure

Surgical management of ectopic pregnancy remains the gold standard treatment, thanks to the improvement of diagnostic methods that allow most patients to undergo elective surgery rather than the emergency one. Laparoscopy is the gold standard for surgical management of EP and represents the least invasive and most accurate approach for the patient[17,18]. Laparotomy is only performed when laparoscopy is not executable for technical, logistical, or medical reasons, similar to cases of tubal EP[19,20]. Alternative methods, such as arterial embolization, followed by intramuscular methotrexate injection, may be an option in some cases where surgical access may be difficult due to the location of the ectopic POC, although in current literature, there are very few cases successfully treated by this interventional radiologic method[21].

The diagnosis of this obstetrical condition requires specific medical skills because the ultrasound approach for abdominal ectopic localization, as in the bowel or peritoneal cavity, can be very difficult. Indeed, EP has many mimickers and various imaging pitfalls, making MRI a crucial diagnostic exam in some cases[22]. Once the decision has been made, surgery must be anatomy-sparing, with the aim of preserving reproductive function: the identification of surrounding structures, such as the bowel, ureters, rectum, cervix, vagina, and major vessels, is essential to reduce post-operative complications[18]. As in our case, where the mass was implanted in the left USL, the principles of "good surgery" remain largely the same as in cases of deep infiltrating endometriosis surgery, in which the ureter must be visualized and even dissected. In similar cases in which a viable IUP coexists with an EP, intrauterine devices should not be manipulated, and laparoscopic manipulation of the uterus should be avoided. Complete resection of the POC should be ensured, and hemostasis may be achieved by suturing, electrocoagulation, or the use of hemostatic agents. The use of tranexamic acid should also be considered. Clinical follow-up of serum beta-hCG levels is mandatory after the procedure until levels become negative. In the recent literature, few reviews have addressed this issue, although one recent review reported a case of EP on the abdominal wall near a cesarean section that was managed laparoscopically[23]. Unfortunately, we could not perform an urgent laparoscopic incision due to the patient's hemodynamic condition. Despite this fact, our case explores and highlights the possible association between IVF techniques and EP. A recent paper reports a patient with a heterotopic USL pregnancy following IVF after a double embryo transfer. She presented with acute onset abdominal pain and was diagnosed with a suspected live tubal ectopic pregnancy with a viable intrauterine pregnancy on ultrasound[24]. The uterosacral ligament (USL) is indeed an uncommon site of implantation for abdominal ectopic pregnancies, and this case highlights the importance of considering non-tubal heterotopic pregnancies in the context of risk factors, including IVF with double ET and abdominal pain, as we did in our clinical case. Furthermore, in another recent case series, the authors reported that the preoperative diagnosis rate of abdominal pregnancy is low, and the most common sites are the pelvic peritoneum and pelvic organs, where the diagnosis can be made with the help of MRI scans[25].

Regarding the various causes of EP, several studies have reported that ART pregnancies are often complicated by various obstetric conditions, and the etiopathogenic mechanisms may include impaired placentation[26]. A recent review discusses publications investigating risk factors associated with EP after IVF, such as a tubal factor of infertility, endometriosis, male factor infertility, and the IVF technologies themselves with associated medical treatment[27]: higher ectopic pregnancy rates could be associated with zygote intrafallopian transfer, assisted hatching, large embryo transfer volume, deep fundal transfer and frozen embryo transfer. Although recent results suggest that the risk of EP with frozen embryo transfer is reassuring, clinicians should be aware of this possibility when performing frozen embryo transfer. Some previous studies reported that higher implantation potential per embryo at the blastocyst stage may increase the risk of EP, compared with cleavage stage[28]. Despite this, a recent study shows a low-

er incidence of ectopic/heterotopic pregnancy in blastocyst-stage frozen embryo transfer compared to cleavage-stage[29]. Although there is a contrast between these studies, we agree with the latest work cited, which explains that there is a better synchronization of the transferred embryo at the blastocyst stage and the receptivity of the endometrium. Indeed, during a normal spontaneous conception, fertilization and transformation into a cleavage-stage embryo occur in the fallopian tube, and the embryo enters the uterine cavity as a morula, where the intricate communication between the embryo (as a blastocyst) and the endometrium allows the implantation[30]. In addition, the risk may increase with the number of embryos transferred[31]. Different hormonal milieu, reproductive health characteristics of infertile women such as tubal dysfunction, technical issues of IVF procedures, and estimated embryo implantation potential are also possible risk factors. Additionally, supra-physiological levels of progesterone may decrease uterine contractility and increase implantation in the uterine cavity in fresh ET cycles compared with frozen ones. The precise contribution of each factor to the development of EP after IVF remains uncertain and requires further investigation.

Among the other potential etiopathogenetic causes involved in EP insurgences, no clear evidence exists linking endometriosis with EP. In our case, the patient has pelvic endometriosis, but she had been in menopause for four years. It is possible that pelvic endometriosis may have impacted the tubal condition, contributing to the tubal malacia for which salpingectomy was performed despite the absence of POC. Indeed, we decided during the surgical procedure to remove the left fallopian tube as it appeared edematous, malacic, and hemorrhagic. Additionally, in this specific case, the optimal fertility strategy may be a future IVF, in which tubes are not necessary for successful embryo implantation, and the choice not to remove malacic tubes is associated with an increased risk of future EP. At the same time, USL is often the site of endometriosis lesions. In another recent case published regarding a ruptured EP at the right USL, the histopathological exam revealed the presence of endometrial tissue directly adjacent to POC, deponing for endometriosis lesion, which suggested a link between the retroperitoneal implantation and endometrial ectopic tissue[32]. Despite the paucity of research examining the influence of endometriosis on EP, identifying the shared molecular mechanisms of both diseases may be relevant from a clinical point of view. Women with endometriosis are often treated for infertility with assisted reproduction techniques (ART), whereas the use of ART alone is one of the most relevant risk factors for EP, putting these patients at a very high risk of developing EP[33].

In conclusion, the current literature documented an association between endometriosis and EP, but the data are not definitive due to the high heterogeneity among studies[34]. Further research and studies involving larger samples are needed to explore different possibilities of EP prevention, especially in patients with endometriosis or in the case of pregnancies obtained by IVF techniques.

Conclusions

This case highlights the importance of considering non-tubal ectopic pregnancies in the clinical context of a woman with elevated beta-HCG levels, abdominal pain, and hemoperitoneum. USL ectopic pregnancies may be due to several risk factors, including double-embryo IVF techniques and pelvic endometriosis, but the main causes involved in the pathogenesis of this condition are still unknown. EP needs to be diagnosed as soon as possible through careful anamnesis and ultrasound examination, and immediate treatment by a multidisciplinary team, including gynecologists, anesthetists, obstetricians, and operating room nurses, is mandatory. The principal aim is to save the patient's life and preserve the possibility of future pregnancies.

Conflict of Interest
The authors declare no conflict of interest.

Funding
The present study did not receive external funding.

Informed Consent
Informed written consent was obtained from the patient for both image sharing and data usage.

Ethics Approval
This study was conducted following the Ethical Principles of the Helsinki Declaration and national laws.

AI Disclosure
No AI was used to conduct or draft this article.

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Availability of Data and Materials
Data is available on request from the corresponding author.

Author's Contributions
F. Bisogni: writing original draft, conceptualization. F. Galanti: writing, review, editing, conceptualization. G. Giampà: methodology. B. Ferraresi: writing original draft, invastigation. D. Miriello: conceptualization. D. Antonaci: methodology. L. Campanella: invastigation. R. Dall'alba: visualization. M. Marinelli: formal analysis. S. Iapaolo: invastigation. L. Antonaci: data curation. A. Rago: data curation. M.C. Schiavi: supervision. V. Spina: supervision. R. Rago: validation, formal analysis. P. Palazzetti: validation, visualization.

Acknowledgments
The authors thank Giuseppe Cerbarano for his assistance with the English language.

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