Case report article

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Challenges in diagnosis and management of heterotopic pregnancy after frozen embryo transfer: A case report

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Background: Heterotopic pregnancy (HP), a rare but high-risk complication where one embryo implants intrauterine while another implants ectopically, presents significant diagnostic and management challenges. The incidence of HP has notably increased in in vitro fertilization (IVF) cycles [1, 3].

Case report: We present a case of a 33-year-old woman with a history of secondary infertility and fallopian tube obstruction, who underwent IVF and frozen embryo transfer (FET). She was diagnosed with heterotopic pregnancy, with one intrauterine pregnancy and one ectopic pregnancy in the ovary, after presenting with abdominal pain and vaginal bleeding. Laparoscopic surgery was successfully performed to remove the ectopic pregnancy while preserving the intrauterine pregnancy [5].

Conclusion: This case highlights the importance of high clinical vigilance and thorough assessment in patients after FET, even when symptoms are nonspecific. Early diagnosis and timely intervention with appropriate treatment strategies are crucial for preserving intrauterine pregnancy and minimizing complications [6, 7].

1. OVERVIEW

Ectopic pregnancy (EP) refers to an abnormal pregnancy in which the fertilized egg implants outside the uterine cavity, with the ampullary segment of the fallopian tube being the most common implantation site, particularly in cases following in vitro fertilisation and embryo transfer (IVF-ET) (Figure 1) [1]. Ectopic pregnancy accounts for 1–2% of all pregnancies, and hemorrhage due to fallopian tube rupture remains the most common cause of maternal mortality during the first trimester [2].

Infertility affects 8–12% of couples worldwide [4]. The relationship between infertility and ectopic pregnancy is complex, as both can simultaneously be causes and consequences of each other. The risk of developing ectopic pregnancy increases after infertility treatment, which may result from the effects of the treatment itself or pre-existing reproductive disorders [1]. However, IVF-ET is a major risk factor for developing ectopic pregnancy, with a 2–3 times higher incidence compared to the general population. IVF can also lead to **heterotopic pregnancy (HP)**, where an ectopic pregnancy coexists with a viable intrauterine pregnancy (IUP).

Heterotopic pregnancy (HP), where one embryo implants in the uterus and another ectopically, is rare but poses significant risks and diagnostic challenges after frozen embryo transfer (FET). Although the natural conception rate of HP is extremely low, approximately 1 in 30,000, the incidence significantly increases in IVF cycles, ranging from 0.09% to 1% (European Medical Journal). Major risk factors include a history of tubal disease, pelvic inflammatory disease, and previous pelvic surgery. Transferring multiple embryos during IVF also elevates this risk [1],[3].

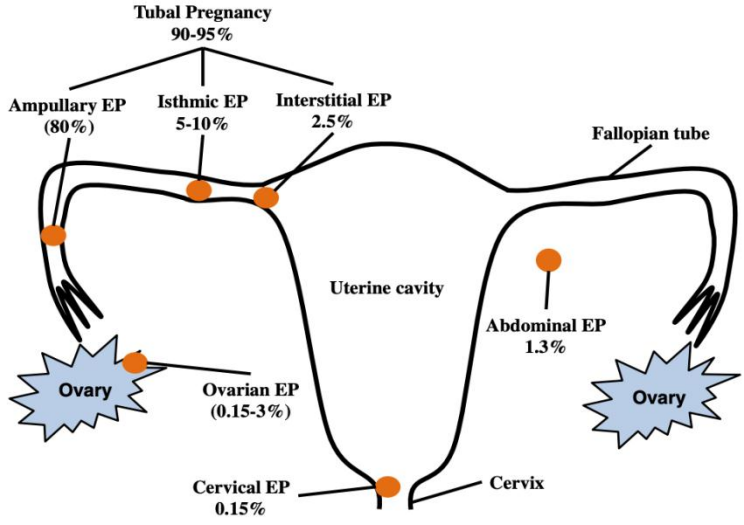

Figure 1. Locations and frequency of ectopic pregnancy after frozen embryo transfer

Diagnosing HP can be challenging because hCG levels may appear within the normal range, and the ectopic pregnancy may be overlooked on ultrasound if an intrauterine pregnancy is already detected and clinical suspicion is low **hCG levels may appear normal**, and ectopic pregnancy may be overlooked on ultrasound [4],[3]. We present a case of heterotopic pregnancy involving an ovarian ectopic pregnancy concurrent with an intrauterine pregnancy following frozen embryo transfer. This article provides a comprehensive overview and insight into preventive measures, diagnostic strategies, and management approaches.

2. CASE REPORT: HETEROTOPIC PREGNANCY WITH ONE INTRAUTERINE AND ONE OVARIAN PREGNANCY AFTER FROZEN EMBRYO TRANSFER

Medical History: A 33-year-old woman presented with secondary infertility (PARA 0020, two previous spontaneous miscarriages within the last two years). Comprehensive evaluation revealed diminished ovarian reserve (AMH 1.4) and right hydrosalpinx. Her husband's semen analysis showed oligospermia and a DNA fragmentation index (DFI) of 32%. After thorough counseling and examination to exclude chromosomal and hormonal abnormalities, the couple opted for in vitro fertilization (IVF). Following ovarian stimulation using the Progestin Primed Ovarian Stimulation (PPOS) protocol starting on day 3 of the menstrual cycle, the patient underwent oocyte retrieval 34.5 hours after administering 10,000 IU of chorionic gonadotropin, yielding eight cumulus-oocyte complexes.

Intracytoplasmic sperm injection (ICSI) was performed, resulting in four grade 2 day-3 embryos. The first frozen embryo transfer of a single day-3 embryo was unsuccessful, with a negative beta-hCG test after two weeks. Subsequently, two day-3 embryos were transferred. Fourteen days post-transfer, serum beta-hCG was 1420 mIU/mL, but transabdominal ultrasound did not show a gestational sac. The endometrium measured approximately 12 mm, with no abnormalities detected. By the fourth week, the patient developed mild abdominal pain and vaginal bleeding. Transvaginal ultrasound revealed an intrauterine gestational sac containing a yolk sac and an embryo with a crown-rump length (CRL) of 2.3 mm and positive cardiac activity. The right adnexa appeared normal, while the left adnexa exhibited a well-defined, heterogeneous mass measuring 22x20 mm with a thick echogenic border and a central anechoic area resembling a yolk sac. Free fluid was noted in the Douglas pouch, with no fluid in the Morison's pouch bilaterally (Figure 2).

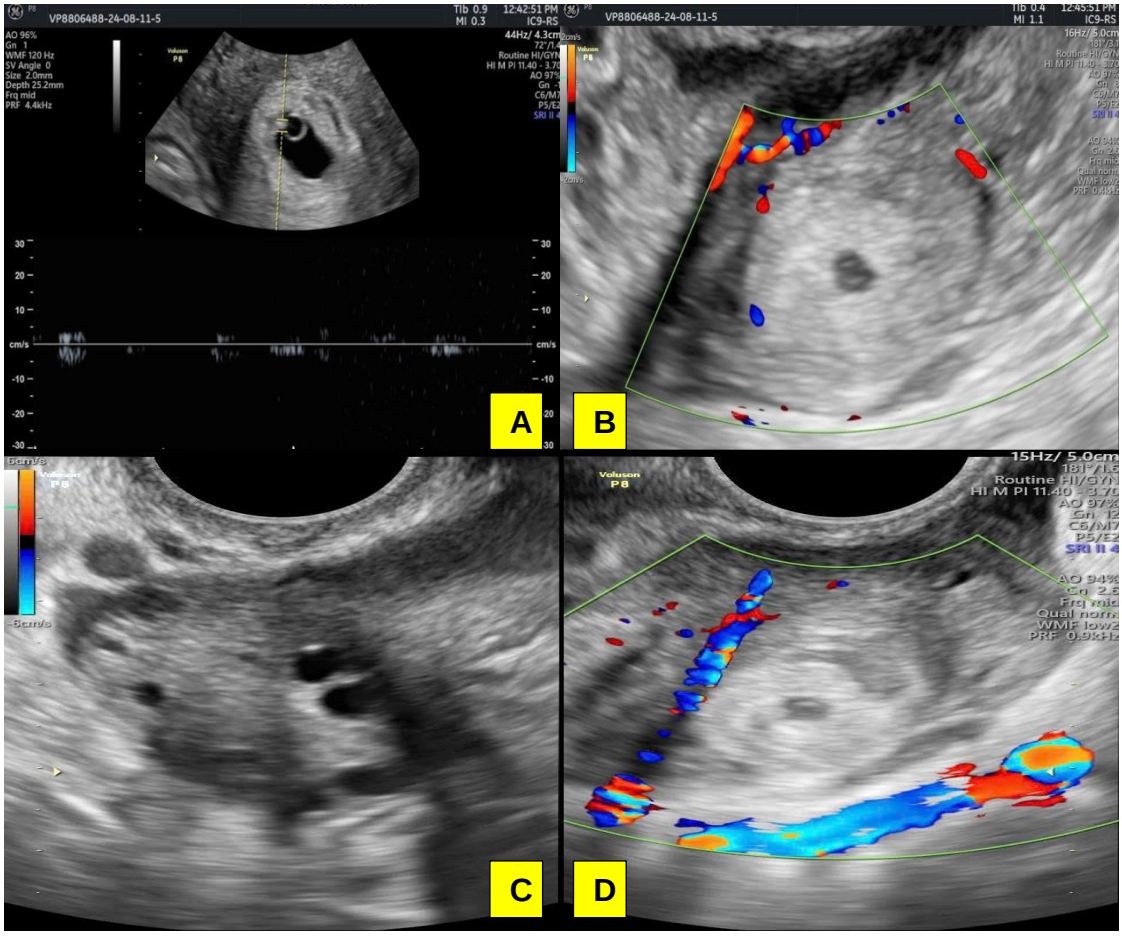

Figure 2. Ultrasound images of heterotopic pregnancy at four weeks after embryo transfer.
(A) Intrauterine pregnancy.
(B, D) Ovarian ectopic pregnancy in the left ovary, showing a thick echogenic border with a yolk sac-like structure inside.
(C) Normal right ovary.

Diagnosis: Combining clinical manifestations, medical history, and laboratory findings, the patient was diagnosed with heterotopic pregnancy, consisting of one intrauterine pregnancy and one ovarian ectopic pregnancy (left ovary).

Management: The patient and her husband were counseled regarding the risks, and they agreed to proceed with laparoscopic surgery to remove the ovarian ectopic pregnancy while attempting to preserve the intrauterine pregnancy.

Surgical Procedure: The patient received prophylactic antibiotics before surgery and underwent general anesthesia with endotracheal intubation. Laparoscopic surgery was performed using one umbilical trocar inserted via the Hasson technique above the umbilicus and two accessory trocars (Figure 4). After aspirating approximately 100 mL of blood from the abdominal cavity, both adnexa were clearly visible. The left adnexa appeared normal, while the right ovary showed a bluish ectopic gestational sac with active bleeding and surrounding blood clots, measuring approximately 2 cm × 3 cm. The left fallopian tube was normal, and the uterus had a regular shape and normal size. After identifying the bleeding ectopic pregnancy, the surgeon excised the ectopic mass from the ovary and meticulously achieved hemostasis.

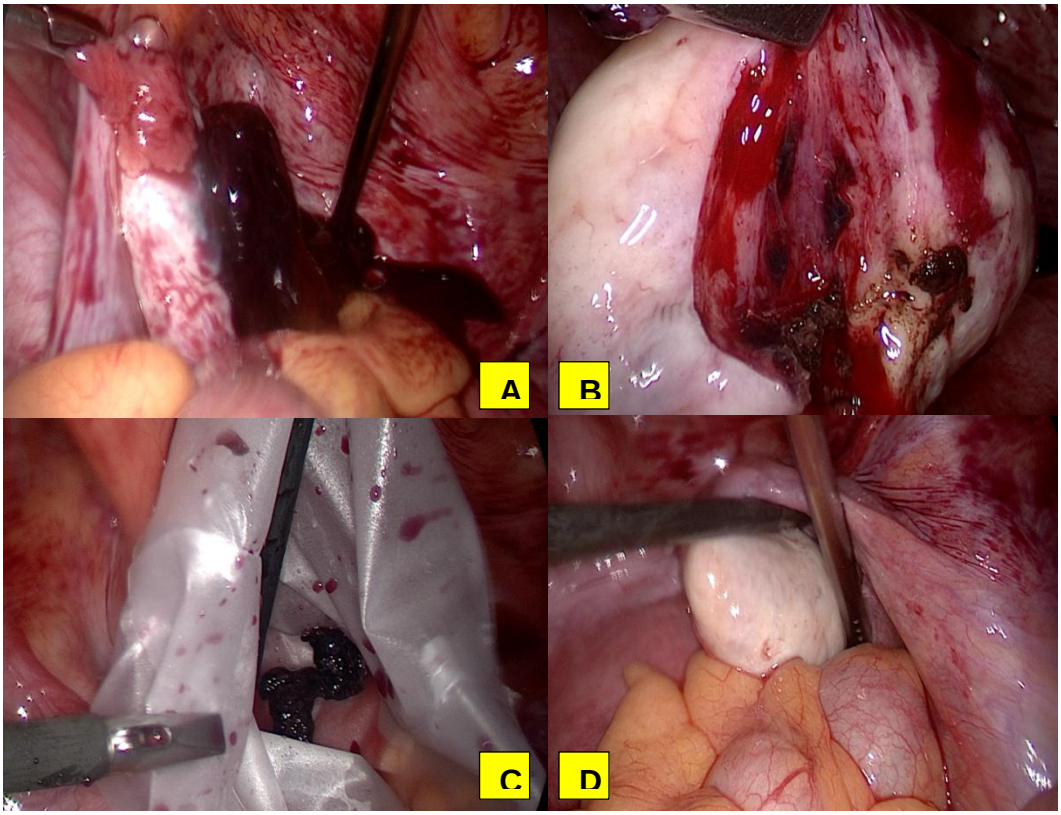

Figure 3. Laparoscopic images of ovarian ectopic pregnancy removal
(A) Bleeding ectopic pregnancy in the left ovary.
(B) Ovary after complete removal of the ectopic mass, with ovarian tissue preserved.
(C) Ectopic pregnancy specimen extracted using an endobag.
(D) Normal right adnexa.

During the surgery, the surgeon minimized uterine manipulation to avoid affecting the intrauterine pregnancy. Additional blood loss during the procedure was approximately 30 mL, and the surgery lasted 35 minutes. The patient recovered well during the remainder of her hospital stay. A follow-up transvaginal ultrasound

showed no free fluid in the abdominal cavity, and the intrauterine embryo continued to develop with normal cardiac activity. The patient was discharged three days after surgery and continued to receive prenatal care throughout the pregnancy. Histopathological examination of the surgical specimen confirmed the diagnosis of ectopic pregnancy (Figure4).

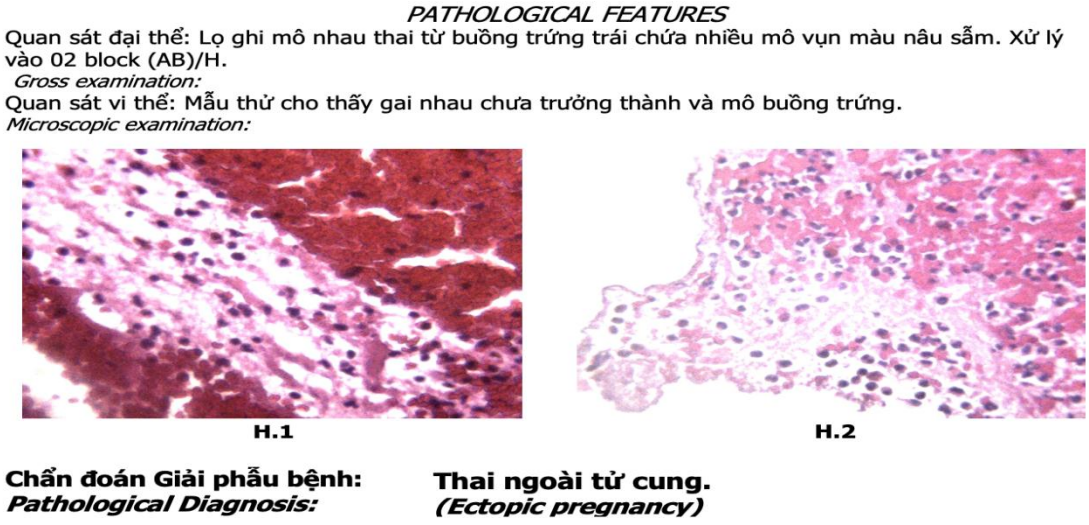

Figure 4. Gross anatomy of the surgical specimen after resection.

Outcome: The intrauterine pregnancy was successfully preserved after surgery and continued to develop normally in the following weeks. Postoperative follow-up showed no complications, and the fetus remained healthy, as confirmed by first and second-trimester screening tests (Figure 5). The pregnancy progressed to full term, and the patient had a successful vaginal delivery at 39 weeks and 4 days. The baby was born healthy, weighing 3,340 grams, with no immediate complications following birth.

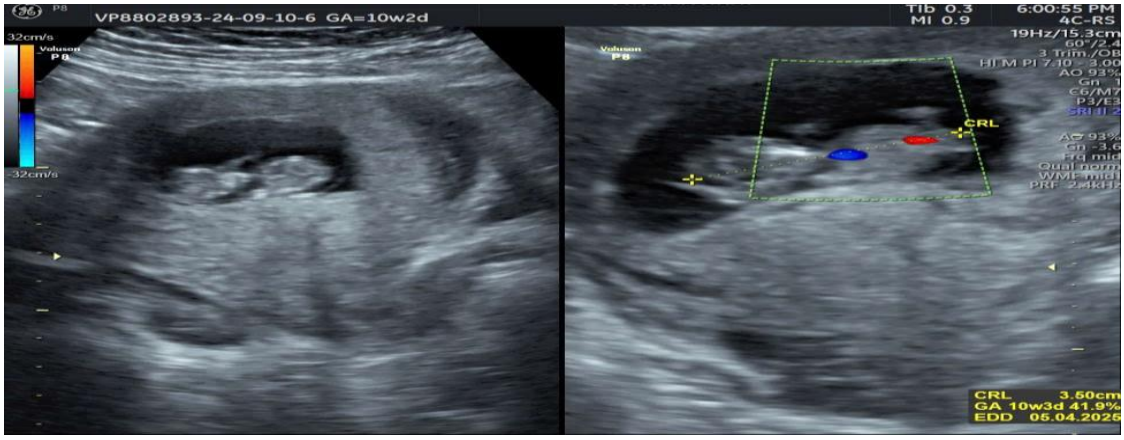

Figure 5. Intrauterine pregnancy developing well after surgery

3. DISCUSSION

Diagnostic Challenges

- Low Incidence and Nonspecific Clinical Presentation: Despite advancements in assisted reproductive technologies, the incidence of heterotopic pregnancy remains low, ranging from 0.02% to 0.5% [5],[6]. This low incidence makes it challenging to recognize and predict this complication, especially in patients without clear risk factors. The clinical presentation is often nonspecific,

making it easy to overlook or misdiagnose as other conditions such as threatened miscarriage or isolated ectopic pregnancy. Common symptoms include vaginal bleeding and acute abdominal pain, similar to those seen in isolated ectopic pregnancy. However, these symptoms can also occur with intrauterine pregnancy, leading to diagnostic confusion. HP is often misdiagnosed as threatened miscarriage due to the simultaneous presence of an intrauterine pregnancy. Unless there is acute abdominal pain or shock related to rupture of the ectopic pregnancy, up to 27.1% to 50% of patients may have no clinical symptoms, further complicating the diagnosis [5] [7]. Studies indicate that the most common symptoms are abdominal pain and vaginal bleeding; however, approximately 16.9% of patients are asymptomatic [1]. Therefore, patients presenting with vaginal bleeding or abdominal pain should be assessed for the possibility of HP, especially after assisted reproductive technologies (ART). Increased ultrasound monitoring is essential for early diagnosis of HP.

Example: A patient who presents with mild lower abdominal pain and light vaginal bleeding after frozen embryo transfer may be initially diagnosed with threatened miscarriage. However, without thorough ultrasound examination and risk factor assessment, an ectopic pregnancy could be overlooked [5]. Multiple studies have shown that tubal pregnancy can still occur even after salpingectomy when combined with IVF-ET (Figure 6). Therefore, heterotopic pregnancy cannot be completely ruled out, even if the fallopian tubes have been removed or ligated [5],[8]. Additionally, uterine injury caused by previous hysteroscopy procedures has been reported as a risk factor for uterine rupture. However, its association with heterotopic pregnancy remains uncertain [8].

Figure 6. Progression of heterotopic pregnancy in a patient undergoing in vitro fertilization (IVF).

- **Role of Beta-hCG Testing**: Although abnormally elevated beta-hCG levels may suggest the possibility of heterotopic pregnancy, they are not sufficient for a definitive diagnosis, as they are nonspecific in cases following embryo transfer. Therefore, beta-hCG testing should be combined with ultrasound and other imaging methods to ensure accurate diagnosis [9]. Example: A patient with rapidly doubling beta-hCG levels after frozen embryo transfer may have a heterotopic pregnancy. However, this finding could also indicate a normally developing intrauterine pregnancy or, in rare cases, an hCG-producing tumor.
- **Limitations of Ultrasound:** Serial serum beta-hCG measurements are essential for diagnosing ectopic pregnancy. However, they are not sufficient for diagnosing heterotopic pregnancy due to the presence of an intrauterine pregnancy, which can mask the ectopic component. Therefore, ultrasound and other imaging modalities play a critical role in identifying heterotopic pregnancy [10]. Ultrasound is essential to ensure the safety of the intrauterine pregnancy and to accurately diagnose ectopic pregnancy in patients

with HP. The preoperative diagnostic accuracy of ultrasound is reported to be 95.06% [5]. Research indicates that only about 56.9% of patients with HP are suspected of having the condition during their initial ultrasound examination, while the remaining cases present with clinical symptoms. In the past, ultrasound practitioners primarily focused on detecting intrauterine pregnancies due to the low incidence of HP, leading to missed diagnoses. However, with the increasing number of ART patients, careful scanning of both adnexal regions is essential, even when an intrauterine pregnancy is detected. Although ultrasound remains the primary imaging tool, identifying ectopic pregnancies in challenging locations such as the abdomen, cervix, or ovaries can be difficult, particularly in the early stages of pregnancy. In such cases, MRI can be a valuable option to support a definitive diagnosis [5],[7],[3].

• **Other conditions:** such as corpus luteum cysts and endometriomas. HP is typically diagnosed through a combination of clinical symptoms (e.g., abdominal pain, vaginal bleeding) and imaging techniques, including ultrasound and MRI. On ultrasound, HP can be identified by the presence of both an intrauterine pregnancy and an ectopic pregnancy (usually in the adnexa or ovary). Corpus luteum cysts, on the other hand, present as a simple cyst with no fetal components, while endometriomas are typically characterized by a homogeneous, echogenic mass. Beta-hCG levels may also assist in the differentiation, as they tend to rise more rapidly in cases of HP compared to other conditions. Close monitoring and serial imaging are crucial for accurate diagnosis and differentiation [9].

Management Challenges - Difficult Treatment Decisions:

The main treatment options include conservative management, medication, intervention, and surgery. The primary criteria for conservative and medical treatment are stable vital signs, an unruptured ectopic pregnancy, and the absence of adverse effects of current medications on the intrauterine embryo.

The choice of optimal treatment depends not only on clinical factors such as the location and size of the ectopic pregnancy, maternal health, and gestational age but also on the patient's desire to preserve the intrauterine pregnancy [5]. This requires detailed counseling, clear and comprehensive communication between the physician and patient, and psychological support to help the patient make an informed decision in a challenging situation.

One study found that ultrasound-guided fetal reduction is preferred over surgery for patients with concurrent ectopic pregnancy (HP) to preserve the intrauterine pregnancy. Techniques such as aspiration or local injection of methotrexate, potassium chloride, and hypertonic glucose support fetal reduction under ultrasound guidance [11]. This method has the advantage of causing minimal trauma and reducing the effects of anesthesia on the intrauterine pregnancy. However, some experts are concerned that methotrexate may increase the risk of fetal abnormalities. In a report by Liu et al., five cases of ultrasound-guided local injection of absolute ethanol were used to treat HP, with injection doses ranging from 1.0 to 2.5 mL. Among these patients, four were successful, while one experienced miscarriage due to rupture of the ectopic gestational sac [12]. However, another study indicated that the risk of intra-abdominal bleeding following ultrasound-guided fetal reduction was higher compared to laparoscopic surgery [13]. Therefore, clinicians should inform patients of the potential risks associated with this method to prevent threats to maternal and fetal health. Additionally, some authors have proposed selective vascular embolization as an intervention. However, embolization alone is often

ineffective due to collateral blood supply and usually requires combination with medical therapy, and its clinical application remains unclear [14].

Surgical Treatment: Surgery remains the primary treatment for heterotopic pregnancy (HP), with no reported adverse effects on the intrauterine fetus. Studies indicate no statistically significant difference in miscarriage rates between laparotomy and laparoscopy [5]. Current evidence shows that laparoscopic surgery does not increase the risk of maternal or fetal complications and offers advantages such as faster recovery, allowing patients to resume daily activities sooner compared to laparotomy [15]. Previous studies report miscarriage rates of 5.9% after laparotomy and 16.7% after laparoscopy, with no significant difference between the two methods. However, emergency surgery due to spontaneous rupture with intra-abdominal bleeding increases the risk of miscarriage and preterm birth compared to elective surgery [15]. The British Society for Gynaecological Endoscopy (BSGE) and the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines (2019) recommend an intra-abdominal pressure of 20–25 mmHg during insufflation and maintaining 12 mmHg during surgery as safe for the fetus. The Hasson technique is preferred for trocar insertion above the umbilicus to reduce the risk of uterine injury [9]. Concerns about potential adverse effects of anesthesia on the fetus are common. In our study, all patients received general anesthesia, and no cases of congenital anomalies were reported [16].

4. CONCLUSION

Heterotopic pregnancy following frozen embryo transfer remains a complex obstetric scenario that requires close collaboration and high expertise among obstetricians, imaging specialists, and laparoscopic surgeons. This case is quite rare in Vietnam, and currently, there are not many reports or accurate statistics available. However, the incidence of heterotopic pregnancy (HP) following frozen embryo transfer (FET) is generally low but may increase in in vitro fertilization (IVF) cases. Some studies show that the incidence of ectopic pregnancy after IVF ranges from 1.4% to 5.4%, which is higher than the general rate of about 1-2% in natural pregnancies. Clinicians should exercise caution when selecting treatment methods, with laparoscopic surgery being a safe and effective option to remove the ectopic pregnancy without increasing the risk of miscarriage or congenital anomalies in the intrauterine fetus. Early and accurate diagnosis, along with selecting the appropriate treatment method based on scientific evidence and the patient's specific circumstances, is key to minimizing complications and optimizing outcomes for both the mother and fetus.

The proposed screening protocol for heterotopic pregnancy (HP) after frozen embryo transfer (FET) in Vietnam includes a detailed risk assessment to identify high-risk patients, followed by serial beta-hCG testing and transvaginal ultrasound 2 weeks post-FET to confirm intrauterine pregnancy and detect any adnexal masses. Patients should be educated on HP symptoms, with follow-up if any symptoms arise. In unclear cases, MRI may be used. Management should focus on preserving the intrauterine pregnancy through methods like methotrexate or laparoscopic surgery, with close postoperative monitoring to ensure continued fetal development. This approach aims to improve early detection and minimize risks for both mother and fetus.

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