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Case Report

Ectopic Pregnancy Following Transfer of a Frozen Blastocyst Embryo in a Spontaneous Cycle: A Clinical Case Report

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Abstract

Ectopic pregnancy is a serious complication, occurring in 1 to 2% of all pregnancies. The risk is higher in patients with a history of tubal surgery and those undergoing assisted reproductive technology (ART). We report the case of a 35-year-old woman, being treated for infertility, who presented with a recurrent left tubal ectopic pregnancy after frozen embryo transfer and failure of medical treatment with methotrexate. The patient (G6P0) had a gynecological history of several ectopic pregnancies and a right salpingectomy. The medical attempt with methotrexate was complicated by severe neutropenia, contraindicating a second injection. The slow rise in hCG levels and the persistence of a left tubal mass prompted a left laparoscopic salpingectomy. This procedure resulted in complete tubal sterility, making future pregnancies dependent on *in vitro* fertilization (IVF). This observation highlights the complexity of managing recurrent ectopic pregnancies after embryo transfer and the importance of multidisciplinary monitoring.

Keywords: *Ectopic Pregnancy; Blastocyst; Spontaneous Cycle; IVF*

Introduction

Ectopic pregnancy (EP), also referred to as extrauterine pregnancy, is defined as the implantation of an embryo outside the uterine cavity, most commonly within the fallopian tube. It represents an obstetric emergency that may compromise the patient's vital prognosis in the absence of early diagnosis and prompt management [1]. Patients with a history of tubal surgery and those undergoing assisted reproductive technology (ART) present an increased risk of EP, even in the absence of apparent tubal pathology. We report a case of recurrent EP following frozen blastocyst embryo transfer, complicated by failure of medical management and requiring definitive salpingectomy.

Case Report

A 35-year-old patient (G6P0) was followed for secondary infertility. She presented with irregular menstrual cycles ranging from 21 to 50 days and a history of multiple ectopic pregnancies. She was found to have polycystic ovarian morphology (PCOM) on ultrasound.

In 2017, a first left tubal ectopic pregnancy was treated medically with methotrexate, followed by exploratory laparoscopy that revealed hemoperitoneum secondary to tubal abortion. No tubal surgical procedure was performed at that time.

In 2019, the patient underwent three intrauterine insemination (IUI) attempts following ovarian stimulation with FSH. The first two attempts resulted in biochemical pregnancies. The third was complicated by a ruptured right tubal ectopic pregnancy requiring right salpingectomy.

Between 2021 and 2022, two complete IVF cycles were performed using an antagonist protocol. Oocyte retrieval yielded eight oocytes in the first cycle and seven in the second. Prolonged embryo culture was carried out to the blastocyst stage (day 5), followed by vitrification of the obtained embryos and subsequent frozen embryo transfers (FET) performed in natural cycles.

A total of eight embryo transfers were performed. One was complicated by a left tubal ectopic pregnancy requiring laparoscopic salpingectomy after failure of medical treatment. The seven remaining transfers resulted in implantation failure despite satisfactory embryo morphology.

No male factor was identified: the partner had a normal semen analysis and proven fertility, excluding any andrological cause.

Discussion

Ectopic pregnancy following ART remains a rare but feared complication with multifactorial pathophysiology [2,3]. The present case illustrates recurrent EP despite management consistent with current standards, highlighting the complexity of preventing this complication in IVF pathways.

Among the various risk factors described in the literature, tubal history plays a central role. In our case, the patient experienced three confirmed tubal ectopic pregnancies followed by sequential bilateral salpingectomies. These interventions reflect significant tubal damage, responsible for secondary tubal infertility. Post-surgical anatomical alterations may promote retrograde embryo migration and ectopic implantation [2].

Beyond anatomical factors, technical aspects of embryo transfer also play a major role. Caroff., *et al*. (2022) and Hu., *et al*. (2022) demonstrated that embryo deposition depth and post-transfer uterine contractility directly influence the risk of ectopic implantation. Excessively proximal deposition or excessive injection volume may induce reflux of the culture medium toward the uterine cornua and fallopian tube, favoring extrauterine implantation [3,4]. These findings support current recommendations advocating the use of soft catheters, ultrasound-guided transfers, and injection volumes ≤ 20 µL to ensure atraumatic fundal deposition. In our case, despite adherence to these measures, retrograde migration risk cannot be completely excluded.

From an endocrine perspective, controlled ovarian stimulation using an antagonist protocol aims to improve endometrial-embryo synchronization. However, several studies emphasize that this strategy does not entirely eliminate risks related to hormonal hyperstimulation. Hu., *et al*. (2022) demonstrated that highly stimulated fresh cycles result in elevated estrogen levels, potentially impairing endometrial receptivity and increasing uterine contractility [4]. In contrast, frozen embryo transfers performed in natural cycles, within a more physiological hormonal environment, may provide a more stable implantation profile.

Cycle type therefore directly influences EP risk. Huang., *et al*. (2014), in a study including more than 30,000 cycles, reported an EP incidence of 1.01% after FET compared with 1.97% after fresh transfer, supporting a protective effect of FET. This difference may be explained by improved endometrial-embryo synchronization and reduced uterine contractility in unstimulated cycles [2]. However, Naredi., *et al*. (2021) reported no significant difference between fresh and frozen cycles, suggesting the involvement of confounding factors such as transfer technique or pre-existing tubal pathology [5].

Embryonic stage is another determining parameter. Blastocyst-stage transfer (day 5 in our case) allows better alignment with the implantation window and reduces embryo migration time, theoretically limiting the risk of ectopic implantation [6]. Nevertheless, this benefit appears attenuated in patients with severe tubal history, as illustrated here, where EP occurred despite transfer at an advanced embryonic stage.

Finally, persistent implantation failure despite morphologically normal embryos suggests impaired endometrial receptivity. Wang., *et al*. (2024) demonstrated that ovulatory disorders, particularly polycystic ovary syndrome (PCOS), are frequently associated with endometrial-embryo asynchrony and functional alterations of the uterine lining, contributing to recurrent implantation failure [7]. This hypothesis is plausible in our patient, whose irregular cycles and dysovulation may reflect underlying hormonal imbalance affecting the implantation window.

Thus, this case illustrates the convergence of anatomical (tubal), endocrine, and technical factors in the development of recurrent EP following ART. Personalization of the transfer protocol, careful selection of high-risk patients, and optimization of embryo transfer timing appear essential to reduce these risks. Planning a single, ultrasound-guided transfer in a natural cycle, combined with thorough tubal and endometrial evaluation, remains a rational approach to optimize reproductive safety and success [8].

Conclusion

This clinical case highlights the complexity of managing recurrent ectopic pregnancies following frozen embryo transfer, even within a natural cycle. Failure of medical treatment and the necessity for bilateral salpingectomy resulted in definitive tubal infertility, making future reproduction dependent on *in vitro* fertilization.

Multidisciplinary management is essential, including reassessment of stimulation protocols and caution in determining the number of embryos transferred, in order to minimize recurrence risk and optimize success rates. This case further emphasizes the importance of a personalized embryo transfer strategy guided by tubal anatomy, hormonal profile, and the patient's reproductive history.

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