


Rare Unilateral Twin Ectopic Pregnancy After Frozen Embryo Transfer: A Case Report and Literature Review

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Background: Unilateral twin ectopic pregnancy is extremely rare in natural pregnancy, with an incidence rate of only 1 in 200,000–2,500,000, represents a major health risk for reproductive-aged women, leading to even life-threatening complications. There is a lack of data on the prevalence of this rare disease after in-vitro fertilization-embryo transfer (IVF-ET) cycles.

Case Report: We present a case of a 51-year-old woman with rare unilateral twin ectopic pregnancy after frozen embryo transfer treated with bilateral salpingectomy, followed by a review of the literature.

Conclusion: Twin ectopic pregnancy is a very rare type of pregnancy that requires a high index of suspicion to diagnose and treat early to prevent complications and maternal death.

Keywords: twin ectopic, pregnancy, unilateral, rare condition, assisted reproductive technology

Introduction

In-vitro fertilization-embryo transfer (IVF-ET) is an important component of assisted fertility technology, and ectopic pregnancy (EP) is one of the common complications of IVF-ET.¹ The incidence of ectopic pregnancy in ART cycle is 1% ~ 5%, which is more than 2 times higher than that in natural cycle.² Unilateral twin ectopic pregnancy is extremely rare in natural pregnancy, with an incidence rate of only 1 in 200,000–2,500,000, represents a major health risk for reproductive-aged women, leading to even life-threatening complications.^{3,4} Since the first case of unilateral twin tubal pregnancy was reported by De Ott in 1891⁵, an average of one case per year is reported in the literature.⁶ Assisted reproductive technology (ART) is responsible for the increase in twin tubal pregnancy.⁷ The misdiagnosis or delayed diagnosis of EP leads to severe bleeding, hypovolemic shock, and other complications, which are related to the maternal incidence rate and mortality. Fallopian tube destruction due to tubal surgery or inflammation, especially chlamydia infection, is a major risk factor for tubal pregnancy. The quantity and quality of transferred embryos, the control of ovarian stimulation (COS) programs, laboratory conditions, and transfer technologies are considered as possible factors for EP after IVF-embryo transfer (ET).⁸ The accurate management strategy for patients at risk of ectopic pregnancy after IVF-ET has not been established.⁸ This report describes a case of 51-year-old patient with unilateral twin ectopic pregnancy that occurred after embryo transfer.

Case Report

A 51-year-old woman with an 11-year history of secondary infertility was referred to the IVF program. During her first marriage, she gave birth to a baby girl in 1998 and a baby boy in 2001, and had abortions in 2005 and 2008, respectively. She remarried in 2012 and had a salpingography in 2015, which showed that bilateral fallopian tubes were patency. She had no history of abdomino/pelvic surgery or dilation and curettage.

In this treatment cycle, antagonist protocol and recombinant follicle-stimulating hormone (rFSH) stimulation starting from day 3 of the menstrual cycle were used for ovulation induction. Follicular development was monitored by plasma estradiol (E2) and transvaginal ultrasonography (TVUSG). On the 13th day of the cycle, with follicles over 18mm and estradiol levels of 1052 ng/mL, 8000 IU of human chorionic gonadotropin (hCG) was administered. Eight oocytes were retrieved by transvaginal sonographic aspiration 36 hours after hCG. On day 3 of culture, three embryos of the 4- to 8-cell stages were transferred. The procedure was done atraumatically and clearly demonstrated ultrasonographically. The embryos were transferred in a total of 25 μ L of culture medium and the patient received luteal support. Ten days after the transfer of the embryos, the serum β -hCG values are 114.2 U/L. Serial monitoring of serum β -hCG values are shown in Figure 1.

The patient's vital signs were unstable at the emergency room: blood pressure, 76/55mmHg; pulse rate, 77 beats/min. Despite the increase in β -hCG values during the hospital follow-up, 29 days after the embryo transfer, the β -hCG levels were 2408 U/L and the serum progesterone (P4) level was 13.30 ng/mL. Transvaginal ultrasonography revealed no gestational sac in the uterine cavity but 2 gestational sacs with 2 yolk sacs at the left adnexa, the endometrial thickness was 9.5mm, and an unilateral twin ectopic pregnancy was diagnosed (Figure 2). The presence of approximately 9 \times 8mm hypoechoic nodules between the anterior uterine wall muscles suggests the possibility of uterine fibroids (Figure 2). Operative findings showed that there was a 4-cm ectopic mass with active bleeding in the ampulla of the left fallopian tube. She underwent bilateral salpingectomy, and the postoperative course was uncomplicated. Gross pathologic and histologic assessments confirmed the 2 distinct pregnancies at the same tube. The twins were dichorionic and diamniotic (Figure 3). The patient had an uneventful recovery. The levels of β -hCG had returned to below 50 U/L at the 3rd postoperative week (Figure 1).

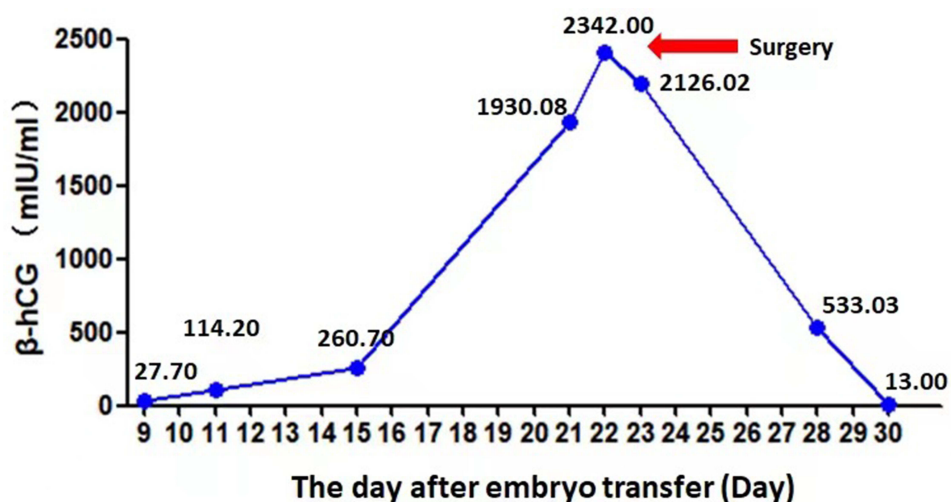


Figure 1 The β -HCG changes after embryo transfer and surgery.

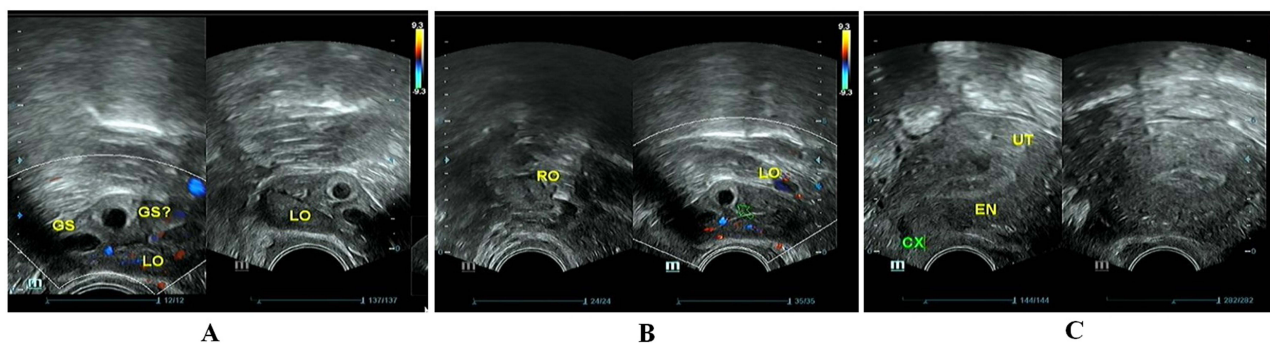


Figure 2 The ultrasonograms before the surgery. (A) 2 gestational sacs with 2 yolk sacs at the left adnexa; (B) Both ovaries were normal; (C) No gestational sac in the uterine cavity and the endometrial thickness was 9.5mm. The presence of approximately 9 \times 8mm hypoechoic nodules between the anterior uterine wall muscles suggests the possibility of uterine fibroids.

Abbreviations: GS, gestational sac; LO, left ovary; RO, right ovary; CX, cervix; EN, endometrium; UT, uterus.

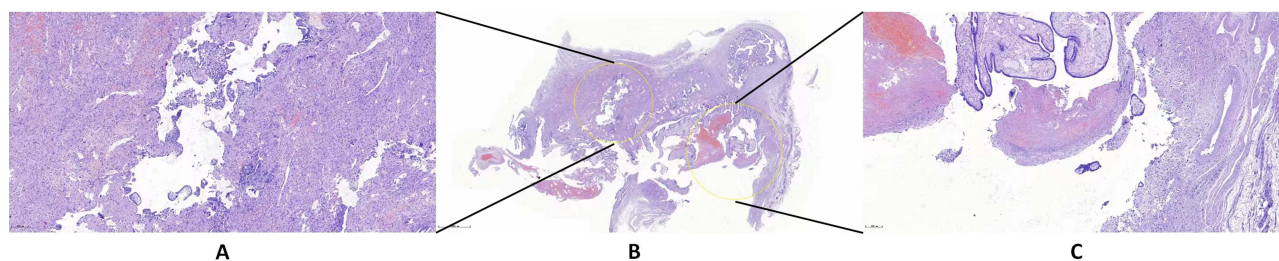


Figure 3 Pathological result of curettage tissue. (A) The first pregnancy after magnification. (B) Histologic assessments confirmed the 2 distinct pregnancies at the same tube. The twins were dichorionic and diamniotic. (C) The second pregnancy after magnification.

Discussion

Ectopic pregnancy refers to implantation of the embryo outside the endometrial cavity, with an incidence of 1–2% in all pregnancy types.⁹ The incidence of ectopic pregnancy accounts for 2.1–9.4% of all clinical pregnancies after IVF.¹⁰ The most common implantation site outside the endometrial cavity is the fallopian tube, accounting for more than 90%.¹¹ Other implantation sites include ovaries, cervix, abdominal cavity, cesarean section scar, or stroma.¹²

Twin ectopic pregnancy occurs in 1:20,000 up to 1:125,000 pregnancies of ectopic pregnancy, and it is an extremely rare condition, which is the implantation of both embryos outside of the endometrial lining.¹² It can usually be implanted on the fallopian tubes, but double ectopic implantation of ovaries, abdomen, cesarean section scars, corneas, and cervix have also been reported.¹³ In the cases of twin tubal pregnancies, most were reported to be bilateral ectopic pregnancy, while a few were unilateral tubal pregnancies. In the present report, the implantation was on the left side of the uterine tube after IVF.

The incidence of ectopic pregnancy appears to increase after IVF-ET treatment compared to natural pregnancies. As the number of IVF procedures continues to increase, the incidence of ectopic pregnancy and bilateral ectopic pregnancy may also rise.¹⁴ Unilateral or bilateral tubal pathology, past pelvic surgery, and pelvic infection are associated with EP. Recent studies have shown that pelvic inflammation and subsequent blockage of the fallopian tubes have been described as risk factors for EP after natural and assisted conception.¹⁵ In addition, risk factors for ectopic pregnancy after IVF include advanced maternal age, pre-existing fallopian tube disease, transferring multiple embryos, poor embryo quality, and loading embryos in high-volume media. According to the theory of “spray effect”, the volume of transport medium should not exceed 20 μ L.¹⁶ In addition to transferring two embryos, poor embryo quality and advanced maternal age were predisposing risk factors for ectopic pregnancy in our present patient.¹⁷ It has also been reported that the use of gonadotropin-releasing hormone (GnRH) analogues may be associated with higher EP rates in the IVF population. In the process of ovulation induced by gonadotropin, high levels of estrogen affect peristaltic movement of fallopian tube and migration of embryos.¹⁸ Some rare ectopic pregnancies in assisted reproduction, such as intrauterine and extrauterine pregnancies, bilateral tubal pregnancies, cervical pregnancies, and ovarian pregnancies, are significantly higher than natural pregnancies.¹⁹

Unilateral tubal twin pregnancies (Table 1) after ICSI-ET have only been reported in a small number of cases.^{20–38} The most reliable technique for diagnosing EP is TVUSG. Intrauterine pregnancy sac loss with elevated β -hCG levels is consistent with abnormal pregnancy.²⁰ Continuous β -hCG levels can also be used for diagnosis. In viable intrauterine pregnancies, the minimum elevation of β -hCG within 2 days is 53%.¹ The minimum reduction in spontaneous abortion within 2 days is 21% to 35%, depending on the initial level.¹ A rise or fall in β -hCG values below these values indicates an ectopic pregnancy.

In this case, an initial rapid rise in β -hCG levels was observed, possibly caused by two sources of hormone production (unilateral twin ectopic pregnancy). This also led to the misconception that it was an intrauterine pregnancy. The combined use of ultrasound, pelvic examination, and follow-up of serum β -hCG levels is a key factor in the appropriate management of current cases. Close follow-up with ultrasound and physical examination helped us to diagnose and treat this case early. Moreover, dual gestational sac trophoblastic activity results in a higher β -hCG than a single gestational sac, which may confuse the clinician’s decision. Delay in diagnosing tubal ectopic pregnancy might lead to severe intraabdominal bleeding and even maternal death. However, in our case, accurate follow-up by expert doctors enabled us to successfully manage patients and clinical doctors in the early stages.

Table 1 Recent Cases for Unilateral Twin Ectopic Pregnancy

Authors	Year	Risk Factors	Clinic Feature	Treatment
Gualandi et al ²⁴	1994	None	Cardiac activity (+)	Laparotomy
E N Göker et al ²³	2001	None	Cardiac activity (+) Unruptured	Laparotomy
S D Sur et al ²⁵	2005	None	Cardiac activity (+) Unruptured	Laparoscopy
Urnsak et al ²²	2006	None	Cardiac activity (-) Unruptured	Laparotomy
Rolle et al ²¹	2006	Multiple sexually transmitted infections	Cardiac activity (-) Unruptured	Laparotomy
Sumate et al ²⁶	2008	None	Cardiac activity (-) Ruptured	Laparotomy
Karadeniz et al ²⁸	2008	INF treatment, Smoke	Cardiac activity (+) Unruptured	Methotrexate
Birte et al ²⁷	2009	None	Cardiac activity (-) Unruptured	Laparoscopy
Murat et al ²⁹	2008	None	Cardiac activity (-) Unruptured	Laparotomy
Karanjoober et al ²⁰	2009	Retained product of conception	Cardiac activity (+) Ruptured	Laparoscopy
Deniz et al ³⁰	2011	None	Cardiac activity (+) Ruptured	Methotrexate
Langoria et al ³¹	2014	Previous Tubal Surgery	Cardiac activity (+) Unruptured	Laparoscopy
Suman et al ³²	2014	Previous Tubal Surgery, Smoke	Cardiac activity (+) Unruptured	Laparoscopy
Ghanbarzadeh et al ³³	2015	Previous Tubal Surgery	Cardiac activity (+) Ruptured	Laparotomy
Chang Kim et al ³⁴	2018	None	Cardiac activity (+) Unruptured	Laparotomy
Betti et al ³⁵		Endometriosis Previous Tubal Surgery	Cardiac activity (-) Unruptured	Methotrexate + Laparoscopy
Hannah et al ⁶	2019	Cesarean section	Cardiac activity (-) Unruptured	Laparoscopy
Chen-June et al ³⁶	2019	None	Cardiac activity (+) Unruptured	Laparotomy
Martin et al ³⁷	2021	None	Cardiac activity (+) Unruptured	Laparotomy
Tadesse et al ⁴	2022	Cesarean section	Cardiac activity (+) Unruptured	Laparotomy

(Continued)

Table I (Continued).

Authors	Year	Risk Factors	Clinic Feature	Treatment
Emine et al ³	2023	None	Cardiac activity (+) Unruptured	Laparoscopy
Raghad et al ³⁸	2023	None	Cardiac activity (-) Unruptured	Laparotomy

Conclusions

In conclusion, ectopic pregnancy, including unilateral twin ectopic pregnancy, is a known risk of IVF. Women who experience irregular vaginal bleeding and lower abdominal pain during the process of abortion after assisted reproductive technology should promptly seek medical treatment and physical examination at a hospital with good conditions, including gynecological examination, quantitative determination of blood and urine HCG, and high-definition color ultrasound examination to determine the clinical pregnancy situation. If no intrauterine pregnancy is found, in order to make a clear diagnosis as soon as possible for patients with indications, appropriate timing for laparoscopic examination can be chosen. This case report highlights the importance of maintaining a high index of suspicion in patients with an acute abdomen and the need for close monitoring and timely surgical intervention. Further research and clinical reports are warranted to improve our understanding of this uncommon condition and optimize its management.

Ethics Approval and Consent to Participate

The protocol was approved by the Ethics Committee of Shanxi Maternal and Child Health Care Hospital (IRB-KY-2017).

Consent for Publication

The patient's written consent has been obtained for publication.

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Disclosure

The authors declare that they have no competing interests.

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