Case Report

Triple tubal ectopic pregnancy resolution with medical management and outcome

Paapa Dasari

Department of Obstetrics and Gynaecology, JIPMER, Puducherry, India

Abstract

Ectopic pregnancy is a life-threatening condition and is rising in incidence due to assisted reproductive techniques in the present era. Three simultaneous implantations in the fallopian tubes is very rare. A 39-year-old G4 A3 was diagnosed to have ectopic pregnancy 42 days after embryo transfer done elsewhere. She had recurrent early pregnancy losses of previous three pregnancies. The first two conceptions were after IUI for prolonged unexplained infertility, and the third pregnancy was spontaneous conception. On the day of admission, she was diagnosed to have two extra uterine gestational sacs of <2 cm on TVS and a β HCG of 4539 mIU/mL. Medical management with variable dose methotrexate was instituted after counseling. Her β HCG rose to 16,125 mIU/L and a review TVS revealed three gestational sacs, two on right side and one on the left side. The third sac measured 1.7 cm × 2.2 cm with small fetal elements after two doses of methotrexate and it was 16,102 mIU/L after completion of one course of methotrexate. She was treated with two doses of 200 mg of mifepristone and was given 2nd course of variable dose of methotrexate and followed by single dose of mifepristone. Her β HCG was 624 mIU/L after 76 days of ET and 33 days of starting therapy. She had spontaneous conception after 2 months of stopping therapy and delivered a healthy baby of 3 kg normally at term.

Keywords: ART, ectopic pregnancy, high β HCG levels, triple tubal ectopic, methotrexate and mifepristone

Address for correspondence: Dr. Paapa Dasari, MD, DGO, FICOG, PDCR, Professor, Department of Obstetrics and Gynaecology, WCH, JIPMER, Puducherry, India. E-mail: dasaripapa@gmail.com

INTRODUCTION

As the prevalence of infertility is increasing, the Assisted Reproductive Techniques (ART) are also on the rise. Ectopic pregnancy is a well-known complication of ART and is life-threatening at times. It may result due to patient factors like pelvic inflammatory disease or due the ART technique itself. It has been reported that ectopic pregnancy occurs in 1–2% of natural concepts and 5% of IVF conceptions. The problem may be in the embryo, genital tract or both. Bilateral synchronus ectopic pregnancies are very rare and the reported incidence varies from1 in 725 to 1 in 1,580 extra uterine pregnancies.[1] Triple ectopic gestation is still rare. Literature search revealed only one such case report.[2] This report describes a rare case of triple ectopic gestation following IVF-ET.

CASE REPORT

A 39-year-old G4 A3 was referred to our Institute from an ART center as ectopic gestation after 42 days of embryo transfer. Her past obstetric history was that she had her first conception 4 years back after an IUI which resulted in first trimester missed abortion and she underwent

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dilatation and curettage for the same. Her second pregnancy was 3 years ago, also after an IUI and resulted in first trimester spontaneous abortion and underwent dilatation and curettage. Third pregnancy was a spontaneous conception and at 52 days, it culminated in spontaneous abortion 2 years ago. She had a consultation with a fertility specialist who treated her with IVF and ET, and the number of embryos transferred was not mentioned in referral slip.

Her complaint during this conception was only pain abdomen. There was no history of fainting attacks, no bleeding per vaginum, no difficulty in micturition or defecation. On examination, she had no palor, pulse was 88/min regular, and BP was 110/70 mm of Hg. Her CVS and RS were normal. Abdomen was soft and there was no guarding and rigidity. Per speculum examination revealed healthy cervix and vagina. Per vaginal examination showed bulky retroverted uterus with cervical motion tenderness and no mass was appreciable in fornices on gentle examination.

Her β HCG was 4539 mIU/L on this 42nd day and a trans-vaginal scan done at admission reported as two ectopic sacs of 2 cm × 2 cm and 1.1 cm × 1.1 cm with minimal free fluid in POD and both ovaries were visualized separately with a normal uterus. She was managed medically employing multidose methotrexate 50 mg/m^2 on days 1, 3, 5, and 7 alternating with folinic acid. Her β HCG after two doses of methotrexate was 16,125 mIU/L and a review TVS revealed three gestational sacs, two on right side and one on the left side. The third sac measured 1.7 cm × 2.2 cm with small fetal elements no CRL could be measured no cardiac activity was observed. The β HCG after completion of one course of methotrexate was 16,102 mIU/L. She was given two doses of tab. Mifepristone 200 mg per day on alternate days. TVS after this treatment showed same size of the sacs and she was given 2nd course of variable dose of methotrexate. Her hemogram, LFT, and RFT were with in normal limits. Her β HCG immediately after this course was 4900 mIU/L a reduction of more than 50% (1/2/2014). TVS did not show any free fluid and the size of the ectopic 1.2 cm × 2.2 cm; 1.2 cm × 2 cm, and 1.7 cm × 2.4 cm. She was given one more dose of tablet mifepristone 200 mg (4/2/2014) and was discharged home (at request) to review with β HCG report after 4 days. The time after ET was 62 days by now. After 66 days of ET and 4 days after stopping medical management her β HCG was 4900 mIU/L (10/2/2014). Her hemogram revealed leucopenia of 2200/mm^3 with platelet count of 314,000. She was hospitalized again and was given inj. Filgastrim 275 mg s.c. daily for 3 days (11/2/2014 to 13/2/2014). Her hemogram normalized after a week and her β HCG was 624 mIU/L (17/2/2014) (76 days after ET). TVS revealed same size of the gestational sacs. The response to methotrexate and mifepristone combination is represented in Table 1.

Table 1: Methotrxate and Mifepristone for medical management of Triple Ectopic

Days after Embryo Transfer	β HCG level mIU/L	Methotrexate/mifepristone
42	4,539	Variable dose methotrexate day 1
45	7,915	Variable dose methotrexate day 4
47	16,125	Variable dose methotrexate day 6
50	16,702	48 h after one course of methotrexate
51	–	Mifepristone 200 mg
52	13,308	2nd course of variable dose methotrexate started
53	–	Mifepristone 200 mg
58		2nd course of variable dose methotrexate over
62	4,900	
66		Mifepristone 200 mg
72	4,300	–
79	624	–

She was counseled not to attempt ART (as she was able to conceive spontaneously) and to take periconceptional folic acid and luteal phase support during the next pregnancy. She had spontaneous conception after 2 months (LMP 13/4/2014) and it was confirmed to be intrauterine gestation at 6 weeks with us. She was managed with inj. HCG 10,000 IU IM once a week till 16 weeks and inj. Proluton 500 mg IM weekly till 36 weeks. She had regular antenatal care at our Institute and delivered a normal healthy child by outlet forceps for fetal distress on 15/1/2015. Alive male child weighed 3 kg with an Apgar of 9/10 at 1 min.

DISCUSSION

The incidence of ectopic pregnancy following IVF is reported to be 4.5% and its incidence is twice following IVF than natural conception. The first treatment cycle by Steptoe and Edwards in IVF has resulted in tubal ectopic pregnancy.[3] Initially though there were only case reports and case series, research has been done to analyze the factors responsible for increased incidence of ectopic pregnancy following ART. A study which analyzed the risk of ectopic pregnancy among women who underwent ART found an incidence of 2.1% of ectopic pregnancies in a very large sample over 3 years (1999–2001) in US. The risk was increased in women with tubal factor infertility,

endometriosis with non-donar IVF-ET. The risk was decreased among ART cycles with donar oocytes, in surrogates and in women with previous live birth. The risk also increased when three or more embryos with high implantation potential were transferred when compared to transfer of two or less.[4]

Revel and colleagues hypothesized that either embryo or fallopian tube participates in implantation of tubal ectopic and studied the role of E-Cadherin expression. They found that tubal ectopic pregnancies following IVF-ET showed double the Cadherin expression in their cytotrophoblastic villi when compared to tubal ectopic pregnancies in non-ART women. They concluded that E-Cadherin expression in the trophoblast implies that preimplantation embryo may be responsible in choosing a favorable implantation site rather than the tubal environment as it lacks E-Cadhein, an important adhesion molecule responsible for implantation.[5]

It was also hypothesized that women who had a previous intrauterine pregnancy were less likely to have ectopic implantations. Chromosomal abnormalities of the embryo and the status/condition of the embryo such as hatching, method of transfer are to be studied further to explore the embryo factors responsible for ectopic pregnancy.[6] In this woman who had intrauterine pregnancy three times earlier, the embryo factor or the force used at the time of transfer may have been responsible. The most common cause in such cases is thought to be the extrusion of embryos through the hydrostatic pressure at the time of embryo transfer.[4] The other factors hypothesized were the wandering of embryos in uterine cavity and their entry in to the fallopian tube. Late expression of adhesion molecules in trophoblasts, low quality of transferred embryos and discordancy of endometrial receptivity at the time of transfer are the other factors.

Early diagnosis is crucial in preventing morbidity and mortality. Tubal ectopic pregnancy can be diagnosed as early as 5 weeks once intrauterine gestational sac is visible and β HCG ≥1500 IU/L. Early diagnosis made it possible to manage ectopic pregnancy medically preserving the integrity of the fallopian tubes. Methotrexate alone is effective when β HCG is ≤3000 IU/L, 14% would require more than one dose 10% would require surgical intervention.[7,8] Triple sac and the high β HCG levels are the challenges in treating this woman medically. Addition of mifepristone has brought down the necessity of more courses of methotrexate. The efficacy of this combination has been proved to be successful. A study which compared methotrexate–mifepristone with methotrexate–placebo for medical management of ectopic pregnancy failed to demonstrate the benefit of addition of mifepristone in general but concluded that the effect of the combination to be limited to ectopic pregnancies with high serum progesterone levels.[9] A Chinese systematic review reported that the combination of methotrexate and mifepristone is more effective and safe than methotrexate alone.[10] Recently a single dose of 200 mg mifepristone combined with 50 μg misoprostol was advocated for medical management of interstitial pregnancy.[11]

The chances of intrauterine pregnancy after medical management of an ectopic pregnancy are reasonably good. A recent study reported a pregnancy rate of 80% after 1 year; however, the live birth rate was 30%.[12] A cumulative intrauterine pregnancy rate of 76% which was equal to that following surgical treatment was found in a population-based study.[13] A systematic review and meta-analysis which assessed ovarian responsiveness to fertility medication in women who were treated with methotrexate for ectopic pregnancy did not show any negative effects.[14] Medical management is safe and does not affect subsequent fertility.

CONCLUSION

The increased risk of ectopic pregnancy needs to be kept in mind when embryo transfer is done and every effort should be made to reduce the same. Addition of mifepristone to methotrexate increases the resolution of ectopic pregnancy and avoids surgical management thus allows preservation of tubal integrity.

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Conflicts of interest

There are no conflicts of interest.

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