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CASE REPORT

A Case Report of Repeat Methotrexate Failure in Ectopic Pregnancy during In Vitro Fertilization

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Abstract

Introduction: Patients who undergo assisted reproductive technology, specifically *in vitro* fertilization (IVF), are at an increased risk of developing ectopic pregnancy. 90% are successfully treated with either single dose or multi-dose methotrexate intervention.

Case presentation: We present a case of a 28-year-old gravid 2 para 0 abortion 1 who underwent IVF resulting in an ectopic pregnancy discovered at 3.5 weeks gestation from embryo transfer date. She subsequently failed methotrexate treatment twice and underwent a salpingectomy.

Discussion: This case adds to the literature of multi-dose methotrexate failure for ectopic pregnancy in IVF patients.

Introduction

Patients who undergo assisted reproductive technology, specifically *in vitro* fertilization (IVF), are at an increased risk of developing ectopic pregnancy. 90% are successfully treated with either single dose or multi-dose methotrexate intervention.

Case

The patient was a 28-year-old-female with a history of infertility seeking *in vitro* fertilization (IVF). The patient had a history of one miscarriage. The patient did not know she was pregnant at the time and only knew once she began bleeding and passing products of conception. The miscarriage did not require medication or surgery.

The patient attempted to conceive without medical assistance with no success. She then underwent 4 rounds of letrozole (Femara) with timed intercourse, also without achieving pregnancy. The patient then sought the help of a Reproductive Endocrinologist. After workup's of both the patient and husband, the diagnosis of unexplained infertility was made. The patient underwent intrauterine insemination with clomiphene (Clomid) twice without success. At this point the patient and her husband had been trying to conceive for a year without pregnancy and decided to start IVF.

The patient was started on standard IVF protocol. The patient's estradiol and progesterone levels were monitored, along with ultrasound, and found to be proceeding normally. Frozen embryo transfer of one single embryo was performed without complication.

9 days after embryo transfer day, the patient's beta hCG level was 66 mIU/ml and then increased to 90 mIU/ml on day 12 after embryo transfer. The patient had an appointment with her OB/GYN on day 15 post transfer to discuss the possibility of miscarriage due to the slow rising beta hCG level. At this time, she was instructed to stop her progesterone and estrogen. The patient experienced light bleeding and cramping abdominal pain on days 19-22.

Follow-up beta hCG level 21 days post embryo transfer showed a dramatic increase in her beta hCG to 1136 mIU/ml. An emergent appointment with the patient's OB/GYN occurred and an ultrasound was performed. An ectopic pregnancy was not visualized; however, it was assumed the patient did in fact have an ectopic pregnancy due to the rapid rise in her beta hCG level. The patient decided to undergo methotrexate (MTX) treatment of her ectopic pregnancy and received

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100 mg total intramuscularly 22 days post embryo transfer.

During the next 24 hours the patient had typical symptoms of nausea, vomiting, loose stools, and headache. 26 days post embryo transfer the patient's beta hCG testing showed an increase to 2496 mIU/ml. The patient and her OB/GYN opted for an additional dosing of MTX; the patient received another 100 mg intramuscularly. She experienced similar symptoms within the next 24 hours. Two days later the patient's beta HCG level was 2613 mIU/ml and an ultrasound was then performed. The ultrasound demonstrated an ectopic pregnancy in the right fallopian tube. Patient then underwent right salpingectomy on day 29 post embryo transfer with a downward trend of beta HCG to 0 by day 18 post right salpingectomy.

Discussion

We feel this case demonstrates failure of MTX in ectopic pregnancy after infertility treatment with IVF. Patients who undergo assisted reproductive technology, specifically IVF, are at an increased risk of developing an ectopic pregnancy with risk at approximately 1.7% [1,2]. Additional risk factors of ectopic pregnancy are fresh embryo transfer, pelvic inflammatory disease, previous appendectomy, tubal pathology, pelvic surgery, and uterine cavity abnormailities [2]. Specifically in the case of IVF population of patients, there is a higher incidence of tubal disease as the underlying cause of the infertility, suggesting an increased risk of tubal pathology in this population [1]. Research has also suggested that altered physiology due to synthetic cycling and retrograde movement of the embryos during IVF create an increased risk for ectopic pregnancy [1]. Of those diagnosed with an ectopic pregnancy following IVF, 90% are successfully treated with either single dose or multi-dose MTX intervention [1]. Methotrexate has been the drug of choice for treatment of ectopic pregnancies, regardless of method of conception, since the 1980s. It works by preventing cell growth in what would have been the developing embryo [3,4]. Furthermore, previous research has found, single dose MTX is only effective in 62.5% of IVF patients with ectopic pregnancies as opposed to 72-85% in non-IVF patients [1].

There are factors which influence a decreased likelihood of failure of MTX in ectopic pregnancy with the use of IVF. Those consist of greater than 3 embryos transferred at one time, previously cryo-preserved embryo transfer of multiples, and adnexal mass < 3.5 cm decreases the likelihood of MTX failure [1]. In general, multiple embryo transfer increases the risk of developing ectopic pregnancy [5]. Interestingly, the beta HCG level for IVF patients at first dose and peak (first dose: 342 IU/L and peak hCG 499 IU/L) were substantially lower for effective MTX use when compared to non-IVF patients (1300-5000 IU/L) [1]. In our patient's case, increasing her likelihood of MTX failure, regardless of dose, was the fact that only one embryo was transferred, also her hCG levels were well out of range of previously documented effectiveness in the IVF population.

Different regimens of MTX use for management of ectopic pregnancy have been proposed, such as increased dosing at first dose or multi-dose treatment, including cases of fetal heart activity, high initial hCG, or gestational mass greater than 3.5 cm [6]. Previous research has shown successful treatment of ectopic pregnancy in up to 95% of the patients, inclusive of IVF and non-IVF patients [6]. A newer approach to MTX use for ectopic pregnancy is the use injecting MTX directly into the amniotic sac either via transvaginal or laparoscopic approach [6]. This method requires visualization of a gestational sac and injection of a higher initial dose at 100 mg, however it has shown an overall success rate of 88.98% [6]. This method would have posed as an option for our patient if a gestational sac was visualized prior to the first dose of MTX. Ultimately, the patient underwent a salpingectomy, which in the case of failure of MTX and rising hCG level, is the recommended treatment option [7].

Conclusion

It is our belief this is a case of multi-dose MTX failure of an ectopic pregnancy from IVF. The beta HCG levels, ultrasound findings, need for a second dose of MTX, and ultimate result of salpingectomy show a failure in management of MTX of an ectopic pregnancy resulting from IVF. All the evidence points toward this conclusion, and this case adds to the literature of MTX failure in ectopic pregnancy resulting from IVF treatment.

Key Points

1. Ectopic pregnancy occurs in 1.7% of pregnancies from IVF treatment.
2. Beta hCG threshold for MTX management in IVF induced ectopic pregnancies is lower than in non-IVF pregnancies.
3. **This case adds to the literature of MTX failure in ectopic pregnancy resulting from IVF treatment.**

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