

# A rare and interesting case of heterotopic cervical pregnancy after intracytoplasmic sperm injection and embryo transfer

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## ABSTRACT

The wide use of assisted reproductive technologies has contributed to the increased risk of ectopic and subsequently heterotopic pregnancy (HP) rate. Cervical ectopic pregnancy is a very rare and life-threatening form of ectopic pregnancy that can also present as HP. We are describing here a case of 34-year-old woman who presented with bleeding heterotopic cervical pregnancy (HCP). The concomitant viable cervical and intrauterine pregnancies were diagnosed at 8 weeks of gestation. Selective fetal reduction was done for cervical pregnancy following which uterine artery embolization was done as a life-saving measure, and subsequently, injection methotrexate was also given. Although cervical component of HCP has the potential for high morbidity due to massive hemorrhage, the mortality rate is low due to early ultrasonographic diagnosis. A high index of suspicion is mandatory for early diagnosis.

**KEY WORDS:** Cervical ectopic pregnancy, hemorrhage, heterotopic cervical pregnancy, methotrexate

## INTRODUCTION

Ectopic pregnancy is a recognized complication of *in vitro* fertilization (IVF) and embryo transfer. The most frequent implantation site of the ectopic pregnancy is in the fallopian tube, most commonly in its ampullary segment (80%). Heterotopic pregnancy (HP) is defined as the presence of an intrauterine pregnancy (IUP) coexisting with an ectopic pregnancy. It is a rare entity with an incidence of 1/10,000–1/50,000 in natural conceptions.<sup>[1,2]</sup> In pregnancies, resulting from assisted reproductive technology (ART), the incidence is greater, ranging from 1/100 to 1/3,600, nearly as high as 1% in some series.<sup>[1]</sup> The big difference in these percentages is attributed to the higher incidence of pelvic inflammatory disease (PID) observed currently resulting in tubal damage as well as ovarian stimulation and transfer of more number of embryos.<sup>[1]</sup> With the increasing use of transvaginal sonography in ART pregnancies, more cases of cervical ectopic pregnancy are being reported.

A recent review has identified only 37 cases reported in English literature, all but four

of which are the result of ART.<sup>[3]</sup> So far, successful management resulting in healthy live birth of the IUP was reported in very few cases of heterotopic cervical pregnancy (HCP).<sup>[3]</sup> The aim of this paper is to emphasize the need for a high index of suspicion of this clinical entity during the routine first-trimester ultrasound examination, even in the presence of an intrauterine gestation, especially so in ART conceptions.

## CASE REPORT

Thirty-four-year-old female with primary infertility had presented to us following one failed IVF cycle done outside 2 years ago for tubal factor. She had a history of

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open myomectomy done several years ago, following which several cycles of ovulation induction (OI) + timed intercourse and OI + interuterine insemination were done. Diagnostic laparoscopy done outside before the first IVF had shown an enlarged uterus, with multiple fibroids and dense adhesions. Right tube was not visualized and left tube was fixed posteriorly.

On evaluation in IRM, her day 2 follicle-stimulating hormone was 4.19 mIU/L, luteinizing hormone was 3.53 mIU/L, and E2 was 35.32 pg/mL. Infections' screening was negative and she was rubella immune. Day 2 scan showed antral follicle count of 9/12 and anterior wall fibroid measuring 42 mm × 38 mm and 16 mm × 15 mm, posterior wall fibroid measuring 30 mm × 30 mm, with a normal appearing cavity. Husband's semen analysis done at our institute showed severe oligo-astheno-teratozoospermia. The patient underwent a diagnostic hysteroscopy and endometrial scratching before intracytoplasmic sperm injection (ICSI). Cavity was found to be normal, with no indentation of any fibroid. The patient underwent controlled ovarian stimulation by long agonist protocol, 13 oocytes were retrieved, 11 M2 and 2 GV. ICSI was done and it resulted in 11 Grade A embryos, which were frozen at 8 cell stage.

Frozen embryo transfer (FET) was done after 8 weeks, 3 embryos 8 cells, Grade A were transferred under ultrasound guidance with an endometrial thickness (ET) of 11.6 mm, at a depth of 1.2 cm. Luteal support was given and beta-human chorionic gonadotropin (beta-hCG) done on day 16 was 956 mIU/mL, which showed a doubling in 48 h and scan done a week later showed an intrauterine gestation of 6 weeks +6 days of gestation had shown an intrauterine live dichorionic diamniotic twin gestation of 6 weeks, with one sac? close to the internal os.

The patient was admitted at 8 weeks of gestation with a diagnosis of bleeding HCP. The beta-hCG on that day was 154,509 mIU/mL and hemoglobin (Hb) was 11.1 g/dl. On per speculum, cervix was ballooned up and blood was seen trickling through the external os. She continued to have mild bleeding overnight, and the Hb done on the following morning was 9.6 g/dl. The patient was extensively counseled and management options were discussed and they opted for selective fetal reduction of the cervical pregnancy using potassium chloride (KCl). The patient started bleeding heavily on the subsequent day and her Hb dropped to 7.5 g/dl. Three units blood was transfused, and once the patient was hemodynamically stable, uterine artery embolization was done using polyvinyl alcohol particles after taking an informed consent. Subsequently, injection methotrexate 50 mg IM was also given 24 h later, she started to expel the products of conception, emergency evacuation was done in view of increased bleeding per

vaginum. She was finally discharged in a stable condition after a week, with a beta-hCG of 2244.8 mIU/mL and Hb of 9 g/dl. She was followed up with weekly beta-hCG, and it became negative after 4 weeks.

She had a second FET after 8 months of the last methotrexate injection, at an ET of 9 mm and a depth of 8 mm and had two embryos transferred in blastocyst stage. In both the transfer cycles, volume of transfer media was 20 µl. Beta-hCG done after 16 days was negative <3.7 mIU/mL. The patient is presently waiting for the next FET cycle.

## DISCUSSION

In ART pregnancies, awareness of the possibility of a HP and its sonographic appearance plays an important role in accurate and timely diagnosis and successful management to help avert potentially fatal consequences. It is reported that approximately 70% of HPs are diagnosed between 5 and 8 weeks of gestation, 20% are between 9 and 10 weeks, and the remaining 10% are after 11 weeks.<sup>[4]</sup> The presence of an intrauterine gestation does not exclude the possibility of a concomitant extra-uterine pregnancy. Careful evaluation of the cervical canal, uterine horns if any, and the adnexa should be a critical part of the early pregnancy ultrasound even after IUP has been confirmed. This is true, especially when the blood hCG level is much higher than expected as was in our case. The cervical component of the HCP can be mistaken for other pathologies such as incomplete abortion, normal pregnancy with low uterine implantation, EP in a cesarean section scar, nabothian cyst, and cervical mass.

The gestational sac in the cervix is typically eccentrically located and is usually round and similar to a normal pregnancy. It may, however, become elliptical or flattened, thus making diagnosis difficult,<sup>[5]</sup> cardiac activity is basically pathognomonic. Histologically, the diagnosis can be made by Rubin's criteria on the surgical specimen where cervical glands are opposite to the trophoblastic tissue, the trophoblastic attachment is below the entrance of the uterine vessels to the uterus or the anterior peritoneal reflection, and fetal elements are absent from the uterine corpus.<sup>[6]</sup> As many pregnancies today are diagnosed early and no hysterectomy is performed, Rubin's criteria can often not be applied. The same holds true in our patient also.

In general, uterine anomalies are a well-known predisposing factor for ectopic pregnancies.<sup>[7]</sup> Other factors predisposing to HP are identical to those predisposing to ectopic pregnancy: Factors related to IVF such as large number of transferred embryos, a transfer near the uterine horn, excessive pressure on the syringe and deep insertion of the catheter during transfer, the quality of the embryos, the hormonal milieu at the moment of transfer, the use

of gonadotropins, the amount of fluid used as media for the embryos, and also adhesions related or not related to endometriosis and PID.<sup>[8,9]</sup> For HPs, transferring four or more embryos during ART is a defined risk factor.<sup>[10]</sup> However, no single risk factor, laboratory test, or combination of these is sensitive or specific enough to predict the occurrence of an HCP. Theoretically, it is possible that after pushing the plunger during ET, the existence of sticky mucus may cause one of the embryos to adhere and slide back to the canal; thus, remnants of cervical mucus may be a risk factor. Some authors have thus proposed that removing the cervical mucus effectively may be a preventive measure to try and avoid cervical pregnancy.

The goals of treatment of HCP are the protection of a coexisting IUP, the minimization of blood loss, and fertility preservation. Since it is a rare entity, there are no standard protocols, but several options exist for the management. Before routine ultrasound was introduced in obstetrics, cervical pregnancy was usually diagnosed during dilatation of the cervical canal and curettage and it usually resulted in life-threatening hemorrhage. As a result of this, most pregnancies of this kind ended in hysterectomy to save the patient's life. The liberal use of high-resolution ultrasound as well as color Doppler in obstetrics has enabled diagnosis of early cervical pregnancy. Thus, various medical methods could be successfully applied in treating early cervical and HCP.

The various medical therapeutic procedures which have been performed include selective fetal reduction procedure by ultrasound-guided KCl or methotrexate injections and systemic methotrexate in some cases.<sup>[11,12]</sup> In the last two decades, cervical pregnancies most commonly have been treated by transvaginal ultrasound-guided selective fetal reduction procedure by injecting KCl into the ectopic component.<sup>[12]</sup> Systemic methotrexate is associated with adverse effects such as thrombocytopenia, leukopenia, elevated liver enzymes, and especially teratogenic effects,<sup>[13]</sup> and thus, a treatment of choice only when our aim is not to preserve the simultaneous IUP. Our patient apart from the cervical pregnancy also had a viable IUP because of which we did not resort to systemic methotrexate as the first line of treatment.

Recently, ligation of the hypogastric artery, embolization of the uterine arteries as well as cerclage of the cervix have also been performed to treat cervical pregnancy. In 2003, Jozwiak *et al.*<sup>[11]</sup> reported a successful hysteroscopic resection of HCP. Uterine artery ligation and embolization may be options when the IUP is not of concern as latter may result in the radiation of the viable IUP, and influence on endometrial receptivity, which could decrease future fertility.<sup>[14]</sup> In our case, we did uterine artery embolization after extensive

counseling as a life-saving measure. Systemic methotrexate was also used in our patient, only once the decision to terminate the pregnancy was finally taken.

Other surgical treatments include suction evacuation, cervical curettage with or without cerclage, and Foley catheter insertion. Foley catheter insertion and cervical cerclage seem universal salvage maneuvers to stop early or late bleeding, whichever technique is used to terminate the cervically located gestation. Nonsurgical treatments are not the right choice for women who are hemodynamically unstable. Laparotomy/laparoscopy may rarely be needed in event of profound bleeding per vaginum.

The minimally invasive approach of embryo aspiration without complete evacuation of the conceptus in a hemodynamically stable patient can be the first treatment of choice in HCP if diagnosed early in pregnancy. However, before this procedure, the patient needs counseling about the risk of the potential complications including bleeding, abortion of the IUP, cervical mass infection which may lead to premature rupture of the membrane, and postpartum bleeding and severe bleeding leading to potential need for emergency procedures including even hysterectomy. For isolated cervical pregnancies, complete evacuation of the pregnancy or systemic methotrexate administration seems a better choice. Advancing technology and early diagnosis of HCP have led to a remarkable improvement in the prognosis of cervical gestations including HCP.

## CONCLUSION

Due to the limited number of cases reported in literature, there is no single universally accepted management protocol for HCP. The therapeutic modality chosen should be able to successfully treat the HCP without causing threat to the concomitant IUP and/or the patient's life. Hence, each patient needs management on individualized basis.

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## Conflicts of interest

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