

Research Letter

Heterotopic triplet pregnancy with an intrauterine, a tubal, and a cervical gestation following *in vitro* fertilization and embryo transfer

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Heterotopic pregnancy is defined as concomitant intrauterine and ectopic pregnancy. In natural conception, it is at a rare rate of 1 in 30,000 pregnancies [1]. However, over the past 3 decades, the rate has increased to 1 in 100 pregnancies, mostly because of the increased use of new reproductive technologies of *in vitro* fertilization and embryo transfer (IVF-ET) treatments in infertile patients [2]. The most common sites of heterotopic ectopic pregnancies, in descending order, occur at the fallopian tube, the cornu, the cesarean scar, the cervix, and the abdomen [3,4].

Cervical heterotopic pregnancy is extremely rare but life-threatening due to the potential risk of massive hemorrhage [5,6]. Diagnosis and treatment are difficult. Conservative treatments include local intrasac injection of potassium chloride or the use of cervical canal tamponade with a Foley catheter balloon for termination of the pregnancy [5]. Hysterectomy is recommended mostly for second- and third-trimester cervical pregnancy, or for uncontrolled bleeding [5].

Making a correct diagnosis of heterotopic pregnancy is difficult and challenging. Symptoms and signs might be misleading and similar to those of an ectopic pregnancy involving the same ectopic site. Laboratory data of β -human chorionic gonadotropin (hCG) in the blood coupled with transvaginal ultrasound are helpful for early diagnosis [4].

Our patient was a 32-year-old Chinese woman, gravida 2, para 1, with an obstetric history of one full-term normal spontaneous delivery. She presented to our hospital with secondary infertility of 10 years, and after a series of

examinations, the diagnosis of tubal factor infertility was made. The patient then underwent an *in vitro* fertilization (IVF) cycle with the long protocol using the gonadotropin-releasing hormone agonist buserelin acetate (Supremon; Hoechst, Frankfurt, Germany). When the diameter of the leading follicle reached 18 mm, 10,000 IU hCG (Profasi; Sero, Geneva, Switzerland) were administered. Thirty-six hours later, five of the seven oocytes were successfully retrieved and fertilized *in vitro*. Three days after oocyte retrieval, four embryos were smoothly transferred into the uterine cavity. Luteal-phase support with progesterone and hCG was given as usual. The serum β -hCG level was 401 mIU/mL on Day 11 after embryo transfer (ET) and rose to 1,941 mIU/mL on Day 14.

The patient reported vaginal bleeding and lower abdominal pain on Day 17 after ET. Transvaginal ultrasound revealed an intrauterine gestational sac measuring 7 mm in diameter, and the serum β -hCG level was 9,885 mIU/mL. Under the impression of threatened abortion, intramuscular progesterone and hCG were administered. Vaginal bleeding and lower abdominal pain were noted intermittently during the hospital stay. On Day 29, repeat transvaginal ultrasound revealed an intrauterine gestational sac measuring 16 mm in diameter with uncertain fetal heart movement. However, on Day 37, the patient suffered from exacerbated pain in the left lower quadrant of the abdomen. Transvaginal ultrasound showed an intrauterine pregnancy with active fetal heartbeat (Fig. 1A) and another gestational sac in the left fallopian tube. Under the impression of heterotopic tubal pregnancy, laparoscopic surgery was performed with general anesthesia on Day 38. It was intraoperatively found that the left fallopian tube was enlarged to 6 cm \times 2 cm \times 2 cm (Fig. 1B). Salpingectomy was performed, and pathologic examination revealed chorionic villi

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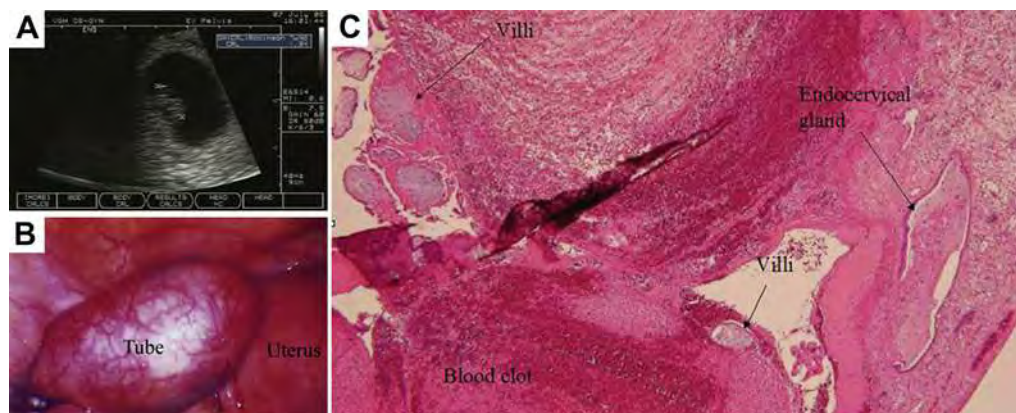


Fig. 1. Heterotopic intrauterine-tubal-cervical pregnancy. (A) Transvaginal ultrasonography showing intrauterine pregnancy at 7 weeks' gestation. (B) Laparoscopy showing left fallopian tube pregnancy at 7 weeks' gestation. (C) Histology of the removed cervical mass indicative of cervical pregnancy (hematoxylin and eosin stain, $\times 40$).

and decidual changes in the left fallopian tube, confirming the diagnosis of heterotopic tubal pregnancy.

However, on Day 51 after ET, the patient experienced sudden and excessive vaginal bleeding. Pelvic examination revealed a protruding cervical mass measuring 2 cm \times 2 cm \times 1.5 cm in size with active bleeding from its surface. Cervical myoma or polyp was initially suspected. Removal of the protruding cervical mass to stop the bleeding was planned. Under spinal anesthesia, the protruding cervical mass was clearly visualized via the speculum and was successfully removed using scissors. The stump of the cervical mass was electrocauterized using a ball electrode connected to a monopolar electrocoagulation device (LEEP System 1000 CooperSurgical Inc., Trumbull, CT, USA) with the power set to 60 W. The procedure lasted 10 minutes and approximately 50 mL of blood was lost. Surprisingly, histologic inspection of the removed cervical mass showed chorionic villi and blood clot attached to the endocervical gland, consistent with the diagnosis of cervical pregnancy (Fig. 1C). The patient was discharged, and her condition was stable. The intrauterine pregnancy continued uneventfully.

Heterotopic pregnancy, defined as concomitant intrauterine and ectopic pregnancy, is an extremely rare event in a spontaneous cycle [1]. However, the incidence of heterotopic pregnancy has been increasing in the past 20 years because of the escalating use of IVF-ET treatments in infertile patients, particularly when multiple embryos are transferred into the uterus [2]. Heterotopic ectopic pregnancies can occur at various sites, such as the fallopian tube, the cornu, the cervix, the abdomen, and the cesarean scar. Of all cases of IVF-ET, heterotopic pregnancy occurs in approximately 1 in 100 pregnancies, and the most common location of ectopic pregnancy is the fallopian tube [2]. Moreover, heterotopic cervical pregnancy, a potentially life-threatening form of ectopic pregnancy, has also been reported in the literature [5]. Triplet, quadruplet, and even quintuplet heterotopic pregnancies have been reported in the literature; however, only two different locations of implantation were found in these cases and the most frequent combination was multiple intrauterine and tubal gestations [7,8]. To our knowledge, there has been no report of

heterotopic triplet pregnancy with an intrauterine, a tubal, and a cervical gestation. This is the first report of such a case.

However, according to the 2007 data from the American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology, ASRM's guidelines for the number of embryos to be transferred in IVF suggested that for patients younger than 35 years and with a more favorable prognosis, consideration should be given to transferring a single embryo only. No more than two embryos should be transferred [9]. High-order multiple pregnancy is an undesirable consequence of assisted reproductive technologies (ART). Multiple gestations lead to an increased risk of complications in both the fetus and the mother [10]. In this case, four embryos should not be transferred for any reason, and we learned a painful lesson from the complications associated with multiple embryo transfer.

Diagnosis of a heterotopic pregnancy can be challenging and a high index of suspicion is mandatory for early diagnosis and appropriate treatment. The symptoms and signs of a heterotopic pregnancy are similar to those of an ectopic pregnancy involving the same ectopic site. The most common presenting symptoms of a tubal pregnancy are abdominal pain and vaginal bleeding [11]. Transvaginal ultrasound and serial serum β -hCG examinations are helpful for early diagnosis. However, patients with cervical ectopic pregnancies often present with painless vaginal bleeding [12]. In these patients, vaginal examination may sometimes disclose gestational tissue protruding from the cervix, but most often, transvaginal ultrasound is necessary for accurate diagnosis. Our patient presented with lower abdominal pain and vaginal bleeding, and heterotopic tubal and intrauterine pregnancy was diagnosed initially by ultrasound examination, followed by laparoscopic salpingectomy. After the operation, vaginal bleeding persisted, and unexpectedly, a protruding cervical mass resembling cervical myoma or polyp was found by vaginal examination, which should be done during the patient's first visit for lower abdominal pain and vaginal bleeding. During removal of the cervical mass, we found that the cervical mass did not arise from an ectopic gestation. Direct removal of the

cervical pregnancy using scissors could lead to uncontrollable hemorrhage; fortunately, the amount of bleeding in our case was small. As we can learn from the current case, cervical pregnancy should be included in the differential diagnosis when a protruding cervical mass is found after ART.

Treatment of ectopic pregnancies is complicated by the simultaneous presence of viable intrauterine pregnancies. With regard to heterotopic tubal pregnancy, surgical intervention with salpingectomy or salpingostomy by either laparotomy or laparoscopy remains the treatment of choice [13]. However, many methods for treating heterotopic cervical pregnancy have been reported. Several conservative therapeutic approaches, including ultrasound-guided aspiration with cervical stay sutures or intracardiac potassium chloride injection, uterine artery embolization, electrodessication, hysteroscopic resection, and cervical cerclage, have successfully treated heterotopic cervical pregnancy without affecting the intrauterine pregnancy [14–16].

In conclusion, we reported a patient with simultaneous intrauterine, tubal, and cervical pregnancies. Suspicion of this rare condition should be aroused in patients undergoing IVF and transfer of multiple embryos when vaginal bleeding or other symptoms persist after successful treatment of one ectopic pregnancy.

Acknowledgments

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