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Case Series

CASE SERIES

Successful management of cervical ectopic pregnancy with embryo reduction: report of three cases

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Abstract

If methotrexate (MTX) fails to resolve cervical ectopic pregnancies (CEP), the remaining surgical options result in the potential loss of the patient's fertility. Therefore, we examined if the embryo reduction technique can resolve the CEP without any complications while conserving the patient's fertility. We report three cases in which CEP didn't respond to MTX but was successfully solved by embryo reduction. Each patient underwent a standard *in vitro* fertilization (IVF) protocol. Once CEP was confirmed, the pregnancy's location, the fetus's size and gestational sac and heartbeat were determined. Afterward, embryo reduction was performed under general anesthesia (operative time: ∼30 min). All patients had successful procedures without any postoperative complications. Since the procedure, one woman was pregnant and delivered, the second has registered a positive β-human chorionic gonadotropin test and the last is waiting for IVF preparation. In summary, embryo reduction is a feasible approach in the management of CEP with favorable fertility outcomes.

INTRODUCTION

Cervical ectopic pregnancy (CEP) is the second common form of ectopic pregnancy after abdominal [1], with an incidence of 1–18 per 20 000 pregnancies [2]. CEP is defined as an ectopic pregnancy in which the embryo implants in the uterine endocervix [3]. Therapeutic modalities include surgical or medical treatments; however, CEP is traditionally considered high risk for maternal hemorrhage. Historically, it has been treated with hysterectomy, which leads to the potential loss of the patient's fertility [4].

Methotrexate (MTX), a folic acid antagonist, has been used as the first-step therapy in treating ectopic pregnancy. In hemodynamically stable patients, MTX is safer, less expensive and effective (80–90%) for early CEP [5]. Even with its superior effectiveness, MTX has been associated with severe complications, and some patients required folinic acid or folic acid to counteract MTX's toxic effects [6]. Nevertheless, when MTX fails, patients undergo surgical remedies: dilatation/evacuation, hysteroscopy and hysterectomy [5].

The main complication of dilatation/evacuation and hysteroscopic resection is a high incidence of severe hemorrhage [7]. Therefore, alternative surgical treatments are required for CEP patients when MTX treatments fail, retaining reproductive potential. Embryo reduction has been used with alternative pathologies and retains reproductive potential [8]. Here, we tested if embryo reduction could be used as an alternative for CEP after MTX failed to resolve the CEP. We report three CEP cases during *in vitro* fertilization (IVF) that were resolved with embryonic reduction without any complications and conserve the patient's fertility.

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To be included in the study, women were attending the clinic for advanced maternal age without any other cause of female infertility and underwent a standardized IVF protocol. They had developed CEP, confirmed by ultrasound, and were unresponsive to MTX. The patients have explained their surgical options and presented with embryo reduction as an alternative, the potential problems associated with embryo reduction and how the procedure has worked with other pathologies. Once the patients agreed, written informed consent was obtained, conducted according to the Declaration of Helsinki. The protocol was approved by the BLINDED, on 18 December 2019.

Embryo transfer, CEP diagnosis and treatment with MTX

Previous to endometrial preparation, hysteroscopic evaluation was performed; the feasibility of uterine cavity access was assessed as well as its size and distension. Moreover, the uterus was evaluated for the absence of polyps or fibroids inside the cavity. The color of the endometrial mucosa was assessed for signs of infection (red dotted) or atrophy (very pale). Lastly, an adequate shaped of the fundus or an arcuate uterus, as well as the ostiums' permeability, were assessed. Once these conditions were identified, a flexible Wallace cannula was inserted through the cervix, ensuring contact with the endometrium.

Embryo transfer was performed on Day 5 after an ultrasound confirmation of the uterine shape/structure as well as the evaluation of the endometrium for a tight trilaminar structure (7–11 mm). Embryo transfer was performed under pelvic ultrasound guidance, with the patient having a partially full bladder. A vaginal mirror was in place, and a vaginal wash was performed with culture medium. Subsequently, the transfer cannula was passed into the internal cervical orifice, at which the biologist was notified, who proceeded to load the embryos. Once the biologist brought the embryos, the soft cannula was removed, and the rigid shirt was left through which the soft cannula that contained the embryos was introduced. It was advanced up to 1.5 cm from the uterine fundus, where the embryos were deposited. The cannula was slowly removed and passed to the biologist to ensure, by microscopy, the embryo's absence. Typically, the embryo was placed in the deepest and thicker zone of the uterus. However, with complicated transfers, a closed cervix, inadequate blood flow/saturation or a minimal view, the embryo can be located more externally.

CEP was diagnosed by transvaginal ultrasound according to the criteria described by Timor-Tritsch [9]. The criteria were (i) presence of gestational sac or placental texture dominantly within the cervix; (ii) absence of intrauterine pregnancy; (iii) visualization of an endometrial stripe and (iv) enlargement of the cervix. MTX was given using the multidose protocol on Days 1, 3, 5 and 7 (i.m.), alternating with calcium folate for detoxication on Days 2, 4, 6 and 8. MTX treatment failure was defined when β-human chorionic gonadotropin (β-hCG) failed to decrease by 15% or the continued fetal heartbeat.

Embryo reduction to resolve the CEP

Before the procedure, an ultrasound was performed using a 5.0-MHz transducer (Panavista-VA GM-2600A, Matsushita, Japan) to determine the location of the pregnancy, the size of the fetus and the gestational sac. Fetal heartbeats were confirmed before starting the procedure. Under general anesthesia, after patients had been placed into the lithotomy position, the vagina was prepared with 10% povidone–iodine and thoroughly rinsed with sterile saline solution. Prophylactic antibiotic (2.0 g cefalotin, i.v.) was administered 1 h before the procedure. Under on-screen sonographic guidance, the fetus was approached transvaginal with a 17-gauge COOK needle for embryo reduction. A cardiac puncture was performed. After ensuring that the fetal heartbeat ceased, the needle was withdrawn. Following the procedure, vaginal hemostasis revision was performed (surgical time = 30 min). A follow-up ultrasound examination was performed after 1 week.

Patient A

Except for advanced maternal age (42 years, Table 1), the patient was healthy (body mass index [BMI] = 25.2 kg/m^2) with no adverse medical history. She was trying to get pregnant for 14 years with no success. She had no history of ectopic pregnancy and no additional risk factors for ectopic pregnancy. She underwent IVF with her ova. Her partner had no problems with his health and sperm quality (normozoospermic). IVF presented with normal parameters (antral follicular count, endometrial thickness, β-hCG serum levels at Day 14). However, at 7.1 weeks, her first ultrasound present with CEP. Ultrasound findings confirmed that the adnexa was at rest. A thickened endometrium with a decidual response, without a gestational sac inside, was observed. A gestational sac was implanted at the cervical level, between the internal and external cervical ostium, presenting with a barrel-shaped bulging cervix. Doppler ultrasound color indicated a positive signal at the cervical level due to embryo implantation. The embryo had cardiac activity. She received MTX and mifepristone; however, postmedical intervention β-hCG serum levels (53 128 mU/ml) indicated that the treatment failed to resolve the CEP, which was confirmed by a second ultrasound. The patient underwent embryo reduction with no complications. Ultrasound confirmed that the gestational sac was devoid of a heartbeat. Afterward, she underwent a second round of IVF with donor ova and gave birth to a healthy boy (weight = 2540 g, length = 47 cm).

Patient B

The patient was healthy (41 years, BMI = 26.0 kg/m^2, Table 1) with no adverse medical history. The patient was trying to get pregnant for 5 years with no success; however, she had one ectopic tubal pregnancy but presented no other additional risk factors for ectopic pregnancy. She underwent IVF with donor ova and her partner's sperm (azoospermia). IVF presented with low antral follicular count ($n = 4$); however, other parameters were normal (endometrial thickness, β-hCG serum levels at Day 14). She complained about vaginal bleeding and pelvic pain, and at 6.3 weeks, her first ultrasound presented with a CEP. Ultrasound findings were similar to Patient A. She received MTX, but the treatment failed to resolve CEP (β-hCG serum levels = 2336 mU/ml, and the fetal heartbeat was present at the second ultrasound.). The patient underwent embryo reduction with no complications. Again, ultrasound confirmed the gestational sac was devoid of a heartbeat.

Patient C

The patient was also healthy (41 years, BMI = 25.3 kg/m^2, Table 1) with no adverse medical history. The patient has been pregnant twice, but both failed to achieve a viable gestation. She had no history of ectopic pregnancy but has had a pelvic history. She underwent IVF with donor ova and her partner's sperm (oligozoospermia). IVF protocol presented with low antral follicular count ($n = 5$); however, other parameters were normal

Table 1. Maternal characteristics and pregnancy outcomes

	Patient A	Patient B	Patient C
Age (years)	42	42	41
Gravity/Parity	0/0	0/0	2/0
History of ectopic pregnancy	none	Tubal ectopic pregnancy	None
Risk factors	none	none	Pelvic surgery
Antral follicular account	Normal ($n = 9$)	Low ($n = 4$)	Low ($n = 5$)
Semen analysis	Normozoospermia	Azoospermia	Oligozoospermia
Ova source	Patient	Egg donation	Egg donation
Endometrial thickness (mm, transfer day)	9.2	10.0	10.0
hCG values (mU/ml)			
Day 14	110	134	53
After MTX treatment	53128	2336	Not applicable
Gestational week at CEP diagnosis	7.1	6.3	6.2
Clinical symptoms	Asymptomatic	Vaginal bleeding/pelvic pain	Asymptomatic
First transvaginal ultrasound	Cervical pregnancy: sac with yolk/embryo with cardiac activity	Cervical pregnancy: sac with yolk/embryo with cardiac activity	1) Intrauterine pregnancy: sac with yolk sac/embryo with cardiac activity 2) Cervical pregnancy: sac with yolk sac and embryo with cardiac activity
MTX	1 mg/kg, intramuscular (2×)	1 mg/kg, intramuscular (3×)	None
Mifepristone	200 mg orally (3×)	None	None
Follow-up transvaginal ultrasound	Cervical pregnancy sac with yolk sac and embryo with cardiac activity.	Cervical pregnancy sac with yolk sac.	Not applicable
Gestational week at embryo reduction	7.5	6.5	6.4
Surgical complications	None	None	None
Postoperative transvaginal ultrasound	Gestational sac: no embryo/yolk sac	Gestational sac: no embryo/yolk sac	1) Intrauterine pregnancy: normal 2) Gestational sac: no embryo/yolk sac
Consecutive IVF cycle	Egg donation	Egg donation	Not applicable
Result of consecutive IVF cycle	Live birth	In preparation	Not applicable

(endometrial thickness, β-hCG serum levels at Day 14). At her first ultrasound, at 6.2 weeks, the patient was asymptomatic; nevertheless, ultrasound findings demonstrated the thickened endometrium. However, two gestational sacs were observed. One intrauterine gestational sac with fundic implantation, whereas the other was implanted at the cervical level. The former presented with normal characteristics of a healthy embryo, whereas the latter presented with a barrel-shaped bulging cervix. It was determined that her pregnancy was heterotopic: (i) intrauterine sac with yolk sac and embryo with cardiac activity and (ii) cervical pregnancy sac with yolk sac and embryo with cardiac activity. Under this condition, we were unable to give MTX. The patient underwent embryo reduction. There was no complication due to the surgery; however, at 8 weeks, the intrauterine pregnancy miscarried.

DISCUSSION

Currently, there are a limited number of treatments for CEP when MTX fails or when it is not an option [1]. Here, we demonstrate that embryo reduction can remove the CEP and retain the patient's fertility.

Even though CEP's etiology remains perplexing, risk factors associated with CEP include smoking, history of pelvic inflammatory disease or previous pelvic surgery, previous uterine or cervical surgery, the use of an intrauterine device, anatomic anomalies, previous ectopic pregnancy, previous cesarean delivery and IVF [10]. Interestingly, the risk of having an ectopic pregnancy during IVF is between 0.9 and 2%. The exact cause for CEP during IVF is believed to be associated with the placement during the embryo transfer procedure [11]; however, few studies have demonstrated this not to be the only factor. CEP during IVF is also associated with ovarian stimulation, several embryos transferred, secondary fertility, treatment for endometriosis and sperm source [12–16].

There is no consensus on the preferred treatment for CEP. Alternative treatments include cerclage with uterine curettage, uterine artery embolization, potassium chloride injection, cervical balloon tamponade, cervical suture and MTX [17–19]. The correct management depends on diagnosis; in general terms, in patients undergoing assisted reproductive technology, the diagnosis is early and is resolved with medical management. The criteria for medical management are serum β-hCG concentrations $<$5000 mIU/ml, a mass $<$ 4 cm, no embryocardia, no ruptures, no signs or symptoms of bleeding or no signs of an acute abdomen. Currently, the primary medical management option is done with intramuscular MTX, with two possible protocols. (i) Single dose (1 mg/kg of weight) in which the β-hCG at 48 h must have decreased by at least 15–30%. If not, a second dose will be administered. (ii) Fixed multidose (1 mg/kg of weight) is administered on Days 1, 3, 5, 7, alternating with folic acid (0.1 mg/kg). As pointed out by Drezett *et al.* [20], even with these alternative treatments, failing to identify CEP early enough can result in the occurrence of severe hemorrhaging or the need for

a hysterectomy, all of which can lead to the loss of the patient's fertility. Here, using embryo reduction, the CEP was resolved while retaining the patient's fertility.

Embryo reduction is typically used in IVF when multiple embryos could diminish the potential of achieving a successful pregnancy [21]. Embryo reduction is a safe and rapid procedure; moreover, it was shown to have minimal effect on the patient's reproduction potential [21]. None of the patients had any adverse effects from the procedure, and for two patients, their fertility was protected. The last patient did have a miscarriage of the intrauterine embryo, but the cause cannot be confirmed to the surgery. One significant difference between our embryo reduction procedure and other methods is the absence of potassium chloride to stop cardiac function. Since CEP's discovery is early, loss of embryonic cardiac function initiates the body's normal process of an early miscarriage thus not requiring the use of potassium.

In conclusion, the embryo reduction technique is a feasible approach in managing CEP, with favorable surgical and long-term fertility outcomes.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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