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## ARTICLE


# Cervico-isthmic pregnancy successfully treated with bipolar resection following methotrexate administration: case report and literature review

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**Abstract** Cervico-isthmic pregnancy is a rare form of ectopic pregnancy associated with a high morbidity and mortality rate. Recent advances in high-resolution ultrasound have made the diagnosis of early cervico-isthmic pregnancies easier. Early diagnosis allows a more conservative therapeutic approach that avoids hysterectomy and preserves fertility. Here is reported a case of viable cervico-isthmic pregnancy successfully treated with resectoscopy after failed systemic and local (hysteroscopic) methotrexate administration. The resectoscopic excision of the cervico-isthmic pregnancy was carried out with the technique of slicing, using a 27 bipolar resectoscope with a 4-mm loop. The procedure was successful with the complete removal of the ectopic pregnancy, while maintaining satisfactory haemostasis. A literature review shows that no consensus exists for the treatment of cervico-isthmic pregnancies. 

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**KEYWORDS:** cervico-isthmic pregnancy, fertility, hysteroscopy, methotrexate

## Introduction

Cervico-isthmic pregnancy is a rare complication of sac implantation, which is poorly described by both pathogenetic and clinical aspects. Normally, the gestational sac implants on the uterine corporal decidua, and only during the second trimester does it occupy the space of the

widened isthmic canal (Strobelt et al., 2001). The incidence of cervico-isthmic pregnancy ranges between 1 in 1000 to 1 in 95,000 pregnancies, which represents nearly 0.15% of all ectopic pregnancies (Cerveira et al., 2005.e7, 2005.e10, 2008; Shinagawa and Nagayama, 1969; Parente et al., 1983; Frates et al., 1994). It is increased in patients with previous Caesarean deliveries and therapeutic abortions, use of

intrauterine device (which may accelerate the passage of the ovum through the uterus), pelvic inflammatory disease, endometriosis, Asherman syndrome and IVF (Kraemer et al., 2008; Cupr et al., 1973; Spitzer et al., 1997; Fylstra and Coffey, 2001; Dicker et al., 1985; Ginsburg et al., 1994; Weyerman et al., 1989).

The criteria for a prenatal sonographic diagnosis of cervico-isthmic pregnancy are unclear, also owing to the rarity of the condition. Therefore, during the first trimester, ultrasonography cannot distinguish the transition between isthmus and cervical canal, but only between isthmus and uterine corpus (Ushakov et al., 1996). Diagnosis and treatment of cervico-isthmic pregnancy have changed in the past 20 years. Before 1980, this condition used to be diagnosed very late, therefore hysterectomy was often the only choice available. Early diagnosis of cervico-isthmic pregnancy has substantially improved with the use of transvaginal ultrasonography and pelvic magnetic resonance imaging. Moreover, the combination of these two techniques allows better definition of disease evolution (Martinelli et al., 2007). Ultrasonography typically shows an empty uterus and a gestational sac within the cervico-isthmic area, invading the anterior or the posterior wall of the cervix (hourglass uterus or dilated cervix). Colour Doppler imaging can be useful to confirm this diagnosis by identifying peri-trophoblastic blood flow (Strobelt et al., 2001).

Advancements in ultrasonography have led to the development of several conservative treatment approaches (medical or surgical) that avoid hysterectomy and preserve fertility (Lin et al., 2008). Medical methods have been developed more recently: intra-amniotic injection of potassium chloride or methotrexate (MTX) and systemic chemotherapy with MTX. Surgical methods include uterine artery ligation and embolization, Foley catheter insertion, cervical curettage with or without cerclage and, more recently, hysteroscopic resection (Kim et al., 2008; Leeman and Wendland, 2009).

This article reports a case of viable cervico-isthmic pregnancy successfully treated with bipolar resectoscopy after failed systemic and local methotrexate administration. Furthermore, different approaches for previously reported cases are discussed.

## Case report

A woman, aged 42 years with a history of two previous Caesarean sections, was referred to the department of gynaecology and obstetrics and pathophysiology of human reproduction with a 2-day history of lower abdominal pain and mild vaginal bleeding. Her last menstrual period had occurred 7 weeks previously. She was referred to the hospital because a viable cervico-isthmic pregnancy was diagnosed during first-line evaluation.

Her vital signs were stable and her haemoglobin concentration was 12.9 mg/dl. Pelvic examination revealed a normal-sized uterus. On speculum examination, the cervix appeared normal, with no evidence of the typical signs of cervical pregnancy (bulky cervix with bluish mucosa, dilated and tortuous submucous vessels). At digital examination, the cervix had normal consistency and length and the lower uterine segment felt mildly distended and softened.

Transvaginal ultrasonography showed a low implantation of the gestational sac, a single embryo with cardiac activity and with a crown-rump length (4.1 mm) consistent with 6 weeks of gestation. The colour Doppler study demonstrated increased flow in the posterior wall of the cervix. The initial serum human chorionic gonadotrophin ( $\beta$ -HCG) concentration was 10,986 mIU/ml. Thus, the diagnosis of cervico-isthmic ectopic pregnancy was confirmed.

The patient was counselled of the high risks of fetal loss, maternal haemorrhage, and hysterectomy associated with this abnormal placental implantation. Thus, she elected to terminate the pregnancy and preserve her fertility. Methods of pregnancy termination were discussed with the patient. She chose medical treatment by intramuscular injection of 50 mg MTX (Cerveira et al., 2005.e7, 2005.e10, 2008; Dotters et al., 1995).

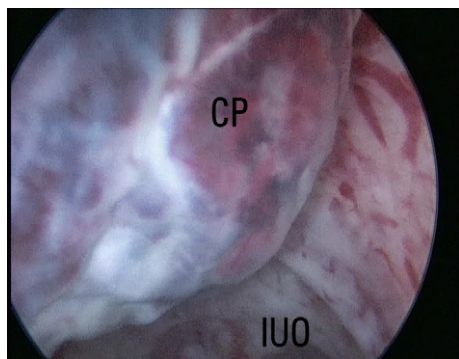
The patient's haematological and biochemical parameters remained stable over the 7 days after treatment. The sonographic scan showed a gestational sac with fetal heart activity and a crown-rump length (7 mm) consistent with 7 weeks of gestation (Figure 1). Furthermore, the patient had several side effects related to the systemic methotrexate such as high fever and gastrointestinal symptoms.

Because of the failure of systemic MTX, diagnostic hysteroscopy was arranged to inject MTX directly within the gestational sac. A vaginoscopic hysteroscopy was performed with a 5-mm continuous-flow office operative hysteroscope with a 2.9-mm rod lens (Bettocchi office hysteroscope size 5; Karl Storz, Tuttlingen, Germany). Neither analgesia nor local anaesthetics were administered to the patient. Distension of the uterine cavity was obtained using normal saline solution, and the intrauterine pressure was automatically controlled by an electronic irrigation and suction device (Endomat; Karl Storz) and was set at 45 mmHg. Hysteroscopy detected a gestational sac on the right posterolateral wall of the Caesarean scar (Figure 2, video of procedure available online). MTX (50 mg) was injected intra-amniotically by means of a 4-Fr needle introduced into the operative channel of the hysteroscope.

The patient was counselled that surgical intervention should be considered if the gestational sac was not expelled or if the size of the gestational mass remained unchanged over the following week.



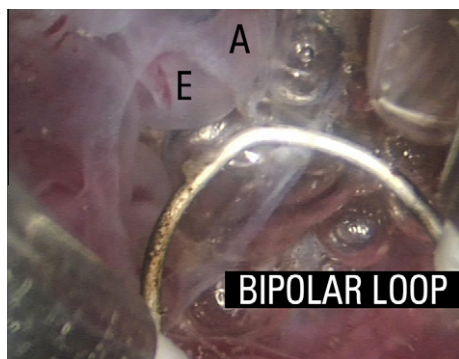
**Figure 1** Transvaginal bidimensional ultrasound showing low implantation of the gestational sac containing a single embryo with heart activity and a crown-rump length (7 mm) consistent with 7 weeks of gestation.



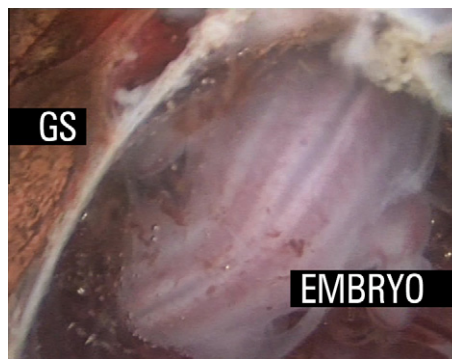
**Figure 2** Ectopic pregnancy detected on the right posterior-lateral wall of the Caesarean scar pouch. CP = cervico-isthmic pregnancy; IUO = internal uterine orifice.

After 7 days, transvaginal ultrasound revealed an unchanged gestational sac with an embryo without heartbeats, but colour signals continued to indicate peri-trophoblastic flow. The haemoglobin concentration of the patient was 9.7 mg/dl, and once again her serum  $\beta$ -HCG concentration did not show any significant decline. Furthermore, the patient started to complain of vaginal bleeding and cramping pain. So the hospital opted for a conservative surgical treatment and the patient agreed to this treatment.

Hysteroscopic resection of the ectopic pregnancy was performed under general anaesthesia; the cervix was dilated up to 10 mm with Hegar's dilators, and a continuous flow 9-mm bipolar resectoscope with a 4-mm loop (Versa-point II, Gynecare; Ethicon, Somerville, NJ, USA) was introduced. The setting of the electro-surgical generator was Versapulse modality with 110 W and 80 DES. Saline solution was used for distention and irrigation of the uterine cavity and the intrauterine pressure was automatically controlled by Endomat. After coagulation of the largest vessels on the base of the gestational sac, it was resected starting from the free edge and progressively moving towards its base (Figures 3 and 4). Particular attention was paid to the resection of the implantation site of the pregnancy, as large vessels were present. A meticulous fluid-balance control was maintained throughout the surgical procedure. The estimated blood loss during the operation was 100 ml. The procedure took approximately 30 min. All the resected



**Figure 3** After opening of gestational sac, the amnios (A) was detected and opened and the embryo (E) was then identified.



**Figure 4** Endoscopic visualization of the dorsal part of the embryo (8 weeks of gestation). GS = gestational sac.

tissue were microscopically examined by a pathologist who confirmed the diagnosis of ectopic pregnancy.

The post-operative course was uneventful with no significant vaginal bleeding. The patient's serum  $\beta$ -HCG concentration declined and her menstruation returned to normal 4 weeks after surgery.

## Discussion

This article reports a rare case of cervico-isthmic pregnancy that was successfully treated by hysteroscopic resection. Although such cases have been previously reported, the novel features of the index case are: (i) the treatment was performed at a relatively advanced gestational age; (ii) MTX was injected by hysteroscopy; and (iii) the surgical procedure was performed after the failure of two previous conservative approaches.

According to the available literature, no consensus exists for the treatment of cervico-isthmic pregnancy. The choice of treatment is based on the patient's condition, their requirements, the risk factors, the availability of the various therapies and the clinician's experience. At present, various conservative treatments can be offered in order to avoid hysterectomy and preserve fertility (Sijanovic et al., 2011). The most commonly used drugs include MTX, mifepristone, actinomycin D and etoposide. MTX is an antimetabolite that inhibits dihydrofolate acid reductase interfering with DNA synthesis, repair and cellular replication. Therefore its action is on actively proliferating tissues, such as malignant cells, bone marrow, fetal cells, skin and buccal and intestinal mucosa. Because of this, it is used for treatment of malignant diseases, rheumatoid arthritis, psoriasis and ectopic pregnancies.

Conservative management of early ectopic pregnancy, using medical treatment alone or in association with minimally invasive procedures, has been widely described as an effective strategy (Brand et al., 1993; Cerveira et al., 2005.e7, 2005.e10, 2008; De Greef et al., 2005; Doters et al., 1995; Gomez Garcia et al., 2012; Heikinheimo et al., 2004; Segna et al., 1990; Sexton and Sharp, 2002; Timor-Tritsch et al., 1994).

Farabow et al. (1983) were the first to describe the use of MTX for treatment of cervical pregnancy. Since then, several reports and case series have cited success rates of more

than 80% in selected cases using MTX therapy. Hung et al. (1998) analysed some prognostic factors affecting the outcome of conservative MTX treatment. He found that MTX therapy was associated with higher failure rates and may need additional interventions in the presence of serum  $\beta$ -HCG concentrations of more than 10,000 IU/l, gestational age >9 weeks, positive fetal cardiac activity or a crown–rump length >10 mm (Cerveira et al., 2005.e7, 2005.e10, 2008; Lin et al., 2008; Hung et al., 1998).

MTX can be administered by two different routes. The systemic route has advantages over local injection in terms of its simplicity and is applicable in more patients. On the other hand, the main benefits associated with intra-amniotic injection are greater effectiveness, shorter treatment period, reduced dosage and toxicity and lower incidence of the main side effects (i.e. fever, gastrointestinal symptoms, thrombocytopenia and leucopenia) (Lin et al., 2008; Pansky, 1999; Kirk et al., 2006; Jeng et al., 2007; Marcovici et al., 1994). The intra-amniotic MTX injection is generally performed under transvaginal ultrasonographic guidance. However, this approach is technically difficult and there is a strong possibility of active bleeding following local injection, caused by rupture of the intra-amniotic membrane (Sijanovic et al., 2011).

In the current case, the first line of treatment chosen was systemic MTX administration. After its failure, the hospital decided to administer MTX by intra-amniotic injection and opted, for the first time, for hysteroscopic injection in order to have a direct visual control of the whole procedure. As soon as the gestational sac was identified, the operator carefully introduced a 4-Fr needle into the operative channel of the hysteroscope and then into an avascular area of the gestational sac. No bleeding was present throughout the procedure.

Surgical techniques are generally applied only when chemotherapy fails in order to prevent two serious complications such as infection (i.e. cervico-isthmic pregnancy tissue retained in the cervix serving as a culture medium for further infection) and intractable bleeding (likely to occur owing to tissue sloughing and necrosis from the atonic cervix). In this case, the partial failure of the MTX therapy and the onset of vaginal bleeding and cramping pain required a further hysteroscopic treatment. Operative hysteroscopy is superior to curettage, because it provides direct visualization of the ectopic location and its vascularity, which is helpful in achieving complete eradication and the accurate cauterization of any bleeding. However, even minimal surgical methods still carry a risk of uncontrolled bleeding, and the patient should be always aware of the possible need for an emergency hysterectomy (Lin et al., 2008; Ash and Farrell, 1996).

Roussis et al. demonstrated hysteroscopic resection of a cervico-isthmic pregnancy for the first time in 1992. Ash and Farrell (1996) reported a 6-week cervical pregnancy that was successfully removed by hysteroscopic resection after ligation of the cervical branch of the uterine artery at the junction between the cervix and the vagina. Jozwiak et al. (2003) described a woman with a 6-week cervical heterotopic pregnancy, who was treated by hysteroscopy alone, in order to preserve an intrauterine fetus (Lin et al., 2008; Ash and Farrell, 1996; Roussis et al., 1992; Jozwiak et al., 2003).

Surgical treatment of the current case started with coagulation of the largest vessels on the base of the gestational sac. Then, the resectoscopic excision of cervico-isthmic pregnancy was carried out with the technique of slicing. Excision began from the free edge of the mass, progressing in a uniform way towards the base. A 27 bipolar resectoscope with 4-mm loop was used. Versapulse modality was the setting of the electro-surgical generator Versapoint II. The use of bipolar technology was preferred as the use of saline solution reduces the risk of electrolyte imbalance and offers controlled predictable tissue effects while providing excellent haemostasis. These advantages are particularly important when the hysteroscopic surgery is performed within the Caesarean scar pouch where the thickness of the myometrial layer is a few millimetres, with a consequently higher risk of perforation. The index surgical procedure was successful with the complete removal of the ectopic pregnancy, while maintaining satisfactory haemostasis.

In conclusion, the most efficient treatment for cervico-isthmic pregnancy remains uncertain. The incidence of cervico-isthmic pregnancy is very low, making challenging the evaluation of conservative methods with prospective randomized studies. The experience presented here seems to suggest that, in order to preserve fertility of women with cervico-isthmic pregnancy, a local combined-hysteroscopic approach is worthy of further evaluation. This approach could be more effective in relatively advanced stages of the first trimester, where systemic MTX shows a high failure rate. In such circumstances, the local administration of MTX, while minimizing side effects and gonadotoxicity of systemic administration, could also maximize the chances of successful hysteroscopic removal of the pregnancy.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.rbmo.2012.10.005>.

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