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Conservative Treatment of Cervico-Isthmic Pregnancy to Preserve Fertility: A Case Report

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ABSTRACT

This report describes the conservative management of a case of cervico-isthmic pregnancy. Options of conservative treatment aimed at preserving fertility in patients with a diagnosis of cervical pregnancy have been described in the literature. While systemic administration of methotrexate represents a conservative and less invasive alternative for hemodynamically stable patients, the case reported here describes the successful conservative treatment of a cervical pregnancy using multiple doses of systemic methotrexate together with the cervical placement of a Foley catheter and inflation of the catheter balloon to staunch the profuse bleeding that occurred as the condition progressed. In patients with a cervical pregnancy, methotrexate is well tolerated, with a minimum of side effects and a high probability that fertility can be preserved.

Keywords

Cervico-isthmic pregnancy, Conservative treatment, Methotrexate.

Introduction

Ectopic pregnancy is defined as the implantation of a blastocyst outside the uterine cavity. Cervico-isthmic pregnancy is a rare form of ectopic pregnancy that accounts for approximately 0.15% of cases, with an estimated incidence of 1/1,000 to 1/18,000 [1-3]. Factors associated with the physiopathology of ectopic pregnancy include pelvic inflammatory disease, with the agent most commonly involved being *Chlamydia trachomatis*, as well as maternal risk factors such as age >35 years, damage to the cervix, uterine malformations, hysterotomy or previous uterine curettage [4].

According to a historical review of the literature published by Schneider, the first case of cervical ectopic pregnancy was published in 1817 by Sir Everard Home, who detected an ectopic pregnancy in the cervical canal during post-mortem examination following diagnosis of the case and profuse bleeding [5]. The term *cervical pregnancy* was first used by Rokitansky in 1860. In 1911, Rubin proposed the first diagnostic criteria for cervical pregnancy based on histopathology findings. In 1941, cervico-isthmic pregnancy was identified as a clinical entity in the literature in the United States and in 1951 Paalman and McElin drew up a list of clinical criteria [6].

Women with a cervico-isthmic pregnancy are at a high risk of potentially lethal bleeding, the control of which may require hysterectomy. The condition presents as heavy, painless vaginal bleeding following a period of amenorrhea, with enlargement and softening of the cervix. Abdominal pain associated with bleeding is present in less than one-third of patients, while pain without bleeding is rare [7].

Risk factors for cervical pregnancy include cervical and uterine abnormalities, previous curettage or Cesarean section, smoking, tubal factor infertility and having undergone assisted reproductive technology, which can play an important role and includes intrauterine and intrafallopian embryo transfer [6,8].

Early diagnosis, improved with the advent of ultrasonography and rapid tests for measuring human chorionic gonadotropin (βhCG), permits a more conservative approach, with a consequent reduction in morbidity and mortality [6].

Currently, with the advances made in the development of new techniques, conservative treatment options have been established that are less invasive, improving mortality rates, avoiding the need to perform hysterectomy and preserving fertility [5,9]. The objective of this paper is to add to the available scientific evidence on the subject by describing a case of cervico-isthmic pregnancy managed using a conservative approach.

This report was approved by the internal review board of the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM) under reference number 4.128.700 / CAAE 32772120.8.0000.5065. The patient gave her consent for publication.

Case Presentation

The patient was a 32-year old woman who reported three previous pregnancies that resulted in one Cesarean delivery due to fetal macrosomia, one normal delivery and one spontaneous abortion. She was healthy, with no allergies and no addictions, and was not using any medication or contraception. She presented at the Emergency Gynecology Unit of the *Santa Casa de Misericórdia Hospital* in Vitória, Espirito Santo, Brazil, complaining of a period of delayed menstruation followed by mild pelvic pain associated with moderately intense vaginal bleeding over the preceding month. Physical examination showed a hemodynamically stable patient in good overall health, with healthy color, flaccid abdomen, no signs of peritonitis, and no heart or lung auscultation abnormalities. Speculum examination revealed an open, epithelialized and hypertrophied cervix, slight bleeding, and amorphous material emanating from the endocervical canal (Figure 1). Digital vaginal examination was not performed at this time to avoid intensifying bleeding. Ultrasonography showed the presence of two anechoic areas measuring 0.7 x 0.5 cm and 0.7 x 0.4 cm, respectively, with an echogenic halo on the posterior endometrial surface and no vascular uptake. The presence of a pseudogestational sac was suspected. There was no fluid in the pouch of Douglas (Figure 2). Ultrasonography was scheduled to be repeated in two weeks. A sample was collected to measure serum levels of βhCG and other follow-up samples were scheduled to be collected every other day.

Two weeks after first examination

Transvaginal ultrasound showed the presence of an echogenic image on the cervix, with a central anechoic area measuring 3.6 x 3.1 x 4 cm and a volume of 24 cm^3, with low-resistance Doppler waveforms. The diagnostic hypotheses were: cervical pregnancy, gestational trophoblastic disease and ovular debris (Figure 3). The most recent quantitative βhCG levels measured every other day were: 47,265.00 mIU/ml (February 26), 43,096.00 mIU/ml (February 28) and 45,693.07 mIU/ml (March 1).

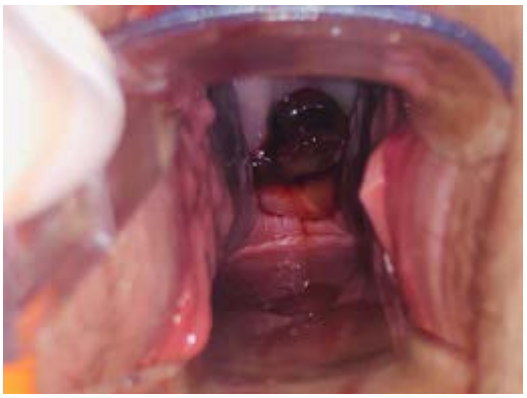

Figure 1: Patient at first evaluation.
Note the cervix epithelized, hypertrophied and open, with slight bleeding and amorphous material emanating from the external cervical os.

Figure 2: Transvaginal ultrasonography performed at the first evaluation on February 12, 2019.
Note the presence of two anechoic areas, measuring 0.7 x 0.5 cm and 0.7 x 0.4 cm, respectively, with an echogenic halo on the posterior layer of the endometrium and no vascular uptake. The presence of a pseudogestational sac was suspected.

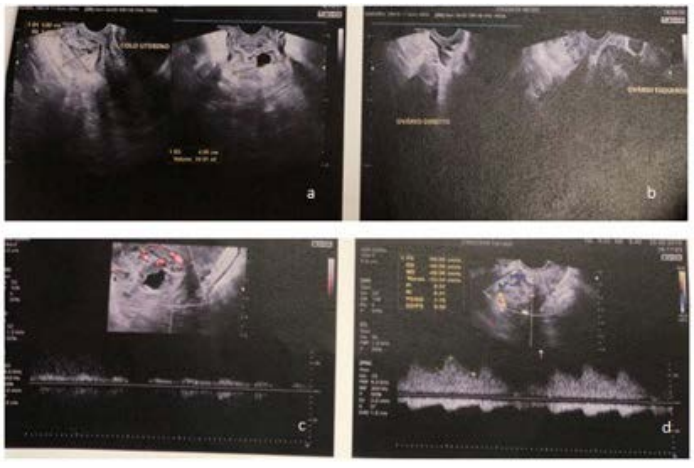

Figure 3: Second transvaginal ultrasonography performed on February 25, 2019.
No notable abnormalities in the ovaries. Note the presence of an echogenic image on the cervix, with a central anechoic area suggestive of a cervical ectopic pregnancy.

Admission to hospital

The patient was admitted to the hospital's gynecology ward on March 1, 2019 to undergo examination after quantitative βhCG testing showed an increase to 45,693.07 mIU/ml. βhCG continued to be performed every other day and hemoglobin and hematocrit were measured daily to determine the best management approach. While increasing levels of quantitative βhCG could indicate worsening of the condition, an abrupt drop in hemoglobin and hematocrit could be indicative of active bleeding. During hospitalization, blood type was identified as O-positive. On March 5, βhCG was 30,865.06 mIU/ml, hemoglobin 10.6 g/dl, and hematocrit 32.6%. VDRL, hepatitis C antibody test (anti-HCV test), hepatitis B surface antigen (HBsAG) and human immunodeficiency virus (HIV) were all non-reactive, while testing for chlamydia was positive. Thyroid stimulating hormone (TSH), free thyroxine (free T4) and a chest x-ray were normal, ruling out the diagnostic possibility of gestational trophoblastic disease. On March 12, another transvaginal ultrasound scan was performed, showing an ectopic gestational sac of 5 cm in diameter in the cervico-isthmic region, with invasion of the myometrium by the trophoblast. The sac contained a single embryo with no detectable fetal cardiac activity and crown-rump length of 15 mm, compatible with embryonic death at nine weeks (Figure 4). These findings led to a diagnosis of cervico-isthmic pregnancy.

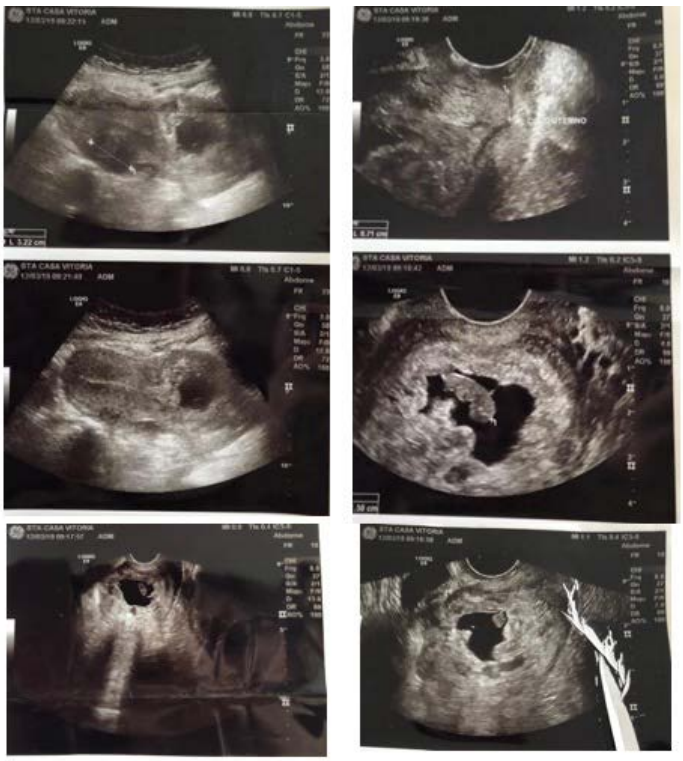

Figure 4: Ultrasonography performed on March 12, 2019.
Note the gestational sac in the cervico-isthmic region.

Since the patient was in good overall health with no complications and laboratory tests confirmed normal kidney and liver function, the gynecology and oncology teams decided to provide non-invasive hospital-based treatment. Therefore, one cycle of methotrexate at a dose of 1 mg/kg was administered on the first, third, fifth and seventh days, interspersed with folinic acid at a dose of 0.1 mg/kg on the second, fourth, sixth and eighth days. On March 15, the patient, already asymptomatic and with no complications, was discharged; however, she continued under the care of the gynecology team as an outpatient, with instructions to return to the hospital every other day for quantitative βhCG measurement.

Second hospital admission

On March 27, the patient returned to hospital with profuse genital bleeding that had begun overnight. Physical examination showed good general health, pale mucosa, skin pallor and perspiration. The external cervical os was open, and there was a discharge of blood clots. Crystalloids were used to stabilize the patient and she was readmitted to hospital. Hemoglobin was 6.1 g/dl and hematocrit 24.1%, requiring a packed red cell transfusion. A cervical Foley catheter was inserted and the balloon inflated to control the profuse bleeding (Figure 5). Quantitative βhCG had decreased to 1,388.72 mIU/ml. Once the bleeding was under control, the patient became stable and there were no further complications. βhCG continued to drop. Speculum examination showed no visible sign of a lesion; therefore, the patient was discharged from hospital (Figure 6).

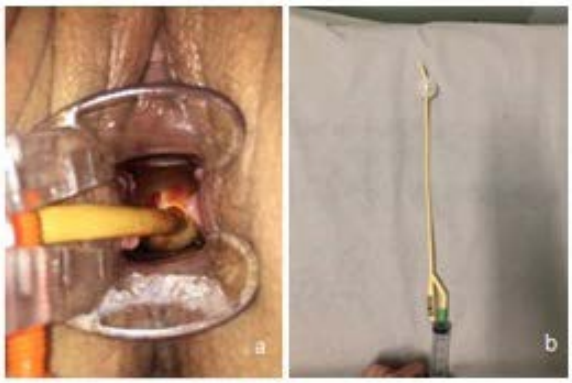

Figure 5: Foley catheter (b) inserted into the cervical canal (a) to control bleeding.

Figure 6: Patient progressing favorably.
No lesions in the cervical canal, and only mild bleeding through the external cervical os.

Follow-up

Transvaginal ultrasound continued to show an ectopic gestational sac in the isthmic region of the cervix, measuring 5.2 x 5.0 x 6.1 cm, with a volume of 84 cm^3, and peripheral vascular Doppler flow. A small subserous nodule of 2.9 cm in diameter, suggestive of a subserous fibroid was detected in the posterior wall. There was no change in any of the other aspects (Figure 7). Quantitative βhCG decreased by approximately 15% a week, taking an average of 2-4 weeks to return to normal levels (Figure 8).

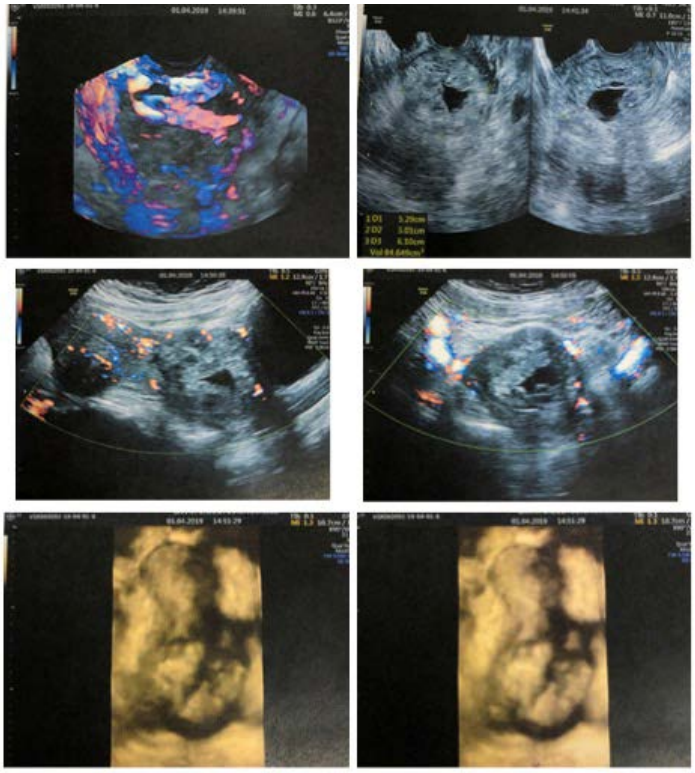

Figure 7: Transvaginal ultrasonography performed on April 1, 2019. *Note the continued presence of an ectopic gestational sac in the cervico-isthmic region measuring 5.2 x 5.0 x 6.1 cm, with a volume of 84 cc, and peripheral Doppler flow.*

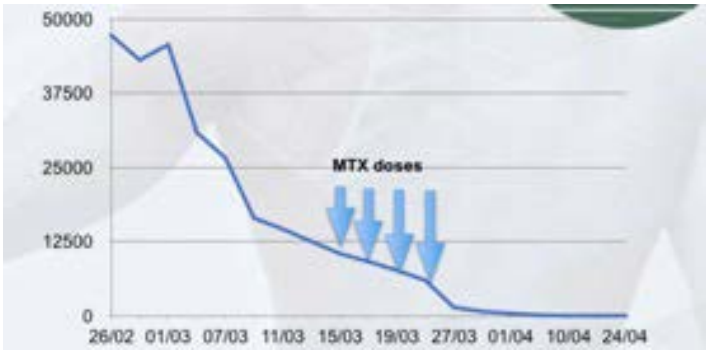

Figure 8: Graph showing the quantitative βhCG measurements. *Note the steady decrease in βhCG levels associated with the doses of methotrexate.*

Quantitative βhCG levels decreased from 47,265.00 mIU/ml on February 26 to normal levels on April 24. Ultrasonography performed on May 10 showed the small subserous nodule on the posterior wall measuring 2.8 cm in diameter, and a small scar from the previous Cesarean section on the anterior wall. The cervix was normal in appearance and the uterus measured 8.6 x 4.9 x 4.7 cm, with a volume of 104.7 cm^3. The endometrium was regular, measuring 1 cm in thickness. The ovaries were normal in appearance. The patient's condition was finally resolved.

Discussion

Cervical pregnancy is a rare form of ectopic pregnancy and is associated with significant morbidity. In addition, there is a negative effect on the patient's fertility [10]. The most commonly accepted clinical criteria for a diagnosis of cervical pregnancy include: painless vaginal bleeding following a period of amenorrhea, a disproportional increase in the cervix, ovular debris in the endocervical canal and a partially open external os [6,11]. The present case meets the criteria required for a diagnosis of cervical pregnancy, which include ultrasonography, imaging and laboratory tests.

The etiology of cervico-isthmic pregnancy remains unknown [12]. Some theories have been put forward to explain ectopic implantation. In 1945, Studdiford suggested that a fertilized egg that crossed the endometrial cavity too quickly could become implanted in the cervical region. In 1950, Ellingson proposed that this type of pregnancy could be associated with unfertilized eggs and in 1968 Iffy speculated that ovulation followed by fertilization of the egg later than usual in the menstrual cycle could result in implantation in the cervical canal conveyed by menstruation [9].

Diagnosis of cervical pregnancy by transvaginal ultrasonography requires demonstrating the presence of a gestational sac in the cervical canal and absence of a gestational sac in the uterine cavity. Care should be taken not to confuse cervical pregnancy with an ongoing spontaneous abortion, with material in the cervical canal [1]. Therefore, color Doppler is essential for a diagnosis of ectopic pregnancy in order to identify peritrophoblastic flow.

Currently, various types of treatment are used in cases of cervical pregnancy; however, for many years hysterectomy was the treatment of choice to control bleeding and save the patient from a negative outcome [12]. Improvement in diagnostic techniques permitted the condition to be detected at increasingly early gestational ages, improving the likelihood of successful conservative treatment that may preserve the patient's fertility [11]. Treatments include chemotherapy with methotrexate, the use of prostaglandins, hysteroscopic resection, hypogastric artery ligation, arterial embolization and cervical cerclage.

In 1983, Farabow et al. were the first to use methotrexate to treat cervical pregnancy. Methotrexate is a chemotherapeutic agent that is able to inhibit the growth of the trophoblast, also inhibiting DNA

synthesis and cell division. It is contraindicated for patients with active kidney or liver disease, leukopenia or thrombocytopenia [5].

Šijanović et al. described a case of cervical pregnancy in a nulliparous patient who was treated unsuccessfully with a single local dose of intra-amniotic methotrexate injection administered under ultrasound guidance. Due to vaginal bleeding caused by the other products of conception, hysteroscopic resection was performed. Those authors concluded that, even taking into account the problems that could occur during treatment with methotrexate, this is the cheapest and most effective treatment for cervical pregnancies. If necessary, the procedure can be combined with other minimally invasive surgical procedures, resulting in satisfactory outcomes. Hysteroscopic resection allows the products of conception to be removed from the cervical canal, causing minimal damage to local tissue and preserving fertility [13].

Murji et al. conducted a retrospective review on the safety and effectiveness of conservative methods for the treatment and management of cervical pregnancies. The study included all 27 cases of cervical pregnancy diagnosed at a tertiary academic healthcare center between January 2002 and July 2014. The median age of the women was 34 years, two-thirds were nulliparous and 44% reported infertility. Mean gestational age following diagnosis was seven weeks. Mean βhCG level was 11,300 mIU/ml (range 610 - 163,700 mIU/ml) and fetal cardiac activity was present in 19 of these pregnancies (70%). Vaginal bleeding was the most common symptom, occurring in 23 cases (85%). Three women were at an acute risk of dying from hemorrhage. All cases were managed conservatively, with successful outcomes and preservation of the uterus in all cases. Systemic methotrexate (single or multi-doses) was the base treatment, together with ultrasound-guided local injection of potassium chloride, uterine artery embolization, transvaginal ligation of the cervical branches of the uterine artery, dilation and curettage, with and without local injection of diluted vasopressin, infiltration and Foley catheter balloon tamponade. That study concluded that systemic methotrexate, alone or in combination with other minimally invasive techniques, can be an effective conservative treatment for cervical pregnancy. The ideal treatment for this population of patients, in whom rates of infertility and nulliparity are high, is one that preserves fertility [14].

Uludag et al. evaluated the conservative treatment of cervical pregnancies in ten women diagnosed between 2010 and 2015. Mean age was 33 years and the women were treated with a systemic or intra-amniotic injection of methotrexate. Eight patients had viable fetuses in which fetal cardiac activity was detected. Six were treated with systemic methotrexate and four with a local injection of methotrexate. One patient who received a systemic injection of methotrexate was transferred for treatment due to the presence of severe oral ulceration and an increase in βhCG levels after the fourth dose. One patient suffered a severe hemorrhage seven days after receiving a local injection of methotrexate. Three patients conceived spontaneously following treatment and went on to deliver full-term infants. The study concluded that the conservative treatment of cervical pregnancy with systemic and local methotrexate was successful insofar as maternal morbidity and fertility are concerned; however, it is vital that the patients are monitored due to the risk of late hemorrhage [15].

Likewise, Kirk et al. performed a retrospective analysis of cervical pregnancies diagnosed in a hospital between 1997 and 2004. Transvaginal ultrasonography was the method used to diagnose the pathology. Serum levels of βhCG were measured at presentation and monitored to determine the success rate. Conservative management was the treatment of choice, with systemic methotrexate being used as a single 50-mg/m^2 dose or at a dose of 1 mg/kg every other day (days 1, 3 and 5), with folinic acid rescue (days 2, 4 and 6). When necessary, intra-amniotic treatment was to be given using 50 mg of methotrexate or 5 mmol/l of potassium chloride. That study concluded that the conservative management of cervical pregnancy is both safe and effective [16].

Methotrexate is not without complications and for this reason must be administered in a hospital setting. Some authors have mentioned issues with the use of methotrexate, particularly the presence of fibrotic tissue around the gestational sac, previous manipulation, and frustrated attempts to perform curettage to remove the lesion, hampering absorption of the drug. Yela and Marchiani reported some complications with the use of methotrexate, including leukopenia, alopecia, stomatitis, nausea and vomiting, liver or kidney failure, genital infection and vaginal hemorrhage [17].

Despite the significant advances made in the diagnosis and treatment of ectopic pregnancy, cervical pregnancy remains a challenge. The earlier it is detected, however, the more likely it is that conservative management will be successful [18]. Systemic administration of methotrexate represents an alternative for hemodynamically stable patients, i.e. a patient with a cervical pregnancy prior to 12 weeks, with no fetal cardiac activity and low serum βhCG levels is more stable from a clinical point of view and can therefore be offered conservative treatment [2]. Yela and Marchiani cited a recent study on the treatment of cervical pregnancy with methotrexate and reported that it is very effective but that when βhCG levels are >20,000 more than one application of methotrexate is required to resolve the situation [17].

In general, conservative treatment involves reducing the risk of hemorrhage, eliminating the gestational products from the cervical canal and preserving the uterus and/or fertility [5]. Curettage is believed to be necessary to reduce the heavy bleeding following the spillage of trophoblastic tissue from the atonic cervix, which occurs as a metabolic effect of methotrexate. In the case reported here, it was decided to use a Foley catheter balloon for 24 hours, which proved effective.

Conclusion

Options of conservative treatment aimed at preserving fertility in patients diagnosed with a cervical pregnancy have been described in the literature. The case reported here describes the successful treatment of a cervical pregnancy using a conservative approach with multiple doses of systemic methotrexate associated

with a Foley catheter balloon to staunch the profuse bleeding. In conclusion, in patients with a cervical ectopic pregnancy, methotrexate is well tolerated, with a minimum of side effects and a high probability of preserving fertility.

Acknowledgements

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