



## CONSERVATIVE MANAGEMENT IN A PATIENT WITH CERVICAL ECTOPIC PREGNANCY IN NARIÑO, COLOMBIA: CASE REPORT AND REVIEW OF THE LITERATURE

### Manejo conservador en una paciente con embarazo ectópico cervical en Nariño, Colombia: reporte de caso y revisión de la literatura

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Received: April 18, 2019 / Accepted: December 21, 2019

### ABSTRACT

**Objectives:** To report a case of cervical pregnancy (CP) treated successfully with a conservative approach, and to conduct a review of the literature on conservative medical and surgical treatment.

**Materials and Methods:** Patient with cervical pregnancy treated pharmacologically with methotrexate (MTX) followed by dilation and curettage, with a satisfactory clinical course. A search of articles was conducted in Medline via PubMed, LILACS, SciElo and Google Scholar using the terms “cervical ectopic pregnancy,” “conservative treatment,” “curettage» «methotrexate,” “uterine

artery embolization,” “hysteroscopy.” Reports and case series were selected of patients with cervical pregnancy diagnosed on ultrasound at any gestational age, subjected to conservative medical or surgical treatment.

**Results:** A total of 22 studies were included; 95 patients with CP treated with MTX were identified, 93 of them successfully treated. The most frequent complication was bleeding in 12%; 26% required complementary surgical treatment. Increasingly, uterine artery embolization (UAE) is carried out preventatively (7 cases) before curettage or treatment with MTX. Hysteroscopy is another recent alternative (20 cases). Abdominal hysterectomy was required in two cases, one of which was a cervico-isthmic pregnancy.

**Conclusions:** MTX continues to be the most frequent treatment strategy. Dilation and curettage with endocervical tamponade may be an option to consider in the emergency management of CP in primary care institutions. In institutions equipped with high complexity technology, uterine artery

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embolization before the surgical procedure, as well as hysteroscopy, are options to be considered. Considering that early diagnosis of CP is now possible, multi-center studies comparing different management options are needed for better assessment of their safety and effectiveness.

**Key words:** Ectopic pregnancy; conservative treatment; curettage; chorionic gonadotropin; fertility (MeSH).

## RESUMEN

**Objetivos:** reportar el caso de un embarazo cervical (EC) que recibió manejo conservador exitoso y realizar una revisión de la literatura sobre el tratamiento médico y quirúrgico conservador.

**Materiales y métodos:** se presenta el caso de una paciente con embarazo cervical, quien recibió manejo farmacológico con metotrexate (MTX) y posterior legrado con evolución clínica satisfactoria. Se realizó una búsqueda de artículos en Medline vía PubMed, LILACS, SciElo y Google académico con los términos: “cervical ectopic pregnancy”, “conservative treatment”, “curettage”, “methotrexate”, “uterine artery embolization” “hysteroscopy”. Se seleccionaron reportes y series de caso, pacientes con embarazo cervical diagnosticado por ultrasonido, de cualquier edad gestacional, sometidas tratamiento médico o quirúrgico conservador.

**Resultados:** se incluyeron 22 estudios; se identificaron 95 pacientes con EC tratados con MTX, con tratamiento exitoso en 93. La complicación más frecuente fue la hemorragia en 12 %; el 26 % requirió tratamiento quirúrgico complementario. Cada vez más, la embolización de arterias uterinas (EAU) se realiza de manera preventiva (7 casos) antes del legrado o del tratamiento con MTX. La histeroscopia es otra alternativa reciente (20 casos). En 2 casos se requirió histerectomía abdominal, uno de los cuales fue un embarazo ístmico cervical.

**Conclusiones:** el tratamiento con MTX sigue siendo el más frecuentemente utilizado. La dilatación y el curetaje con taponamiento endocervical puede ser una opción por considerar en el manejo

de urgencia del EC en instituciones de atención primaria. En instituciones donde se dispone de tecnologías de alta complejidad, la embolización de arterias uterinas previa a los procedimientos quirúrgicos y la histeroscopia son opciones que se deben considerar. Dado que actualmente es posible el diagnóstico temprano del EC, se requieren estudios multicéntricos que comparen las diferentes alternativas de manejo para una mejor evaluación de su seguridad y efectividad.

**Palabras clave:** embarazo ectópico; tratamiento conservador; legrado; gonadotropina coriónica; fertilidad (DeCS).

## INTRODUCTION

Cervical ectopic pregnancy (CP) is defined as a pregnancy implanted in the uterine cervix below the internal os (1). According to Schneider *et al.* (2), Everard Home was the first author to mention cervical ectopic pregnancy in 1817, and it was Rokitansky who coined the term in 1860. Schneider reports that Rubin, in 1911, established four criteria for the diagnosis of this condition: presence of cervical glands opposite to the placental attachment; presence of an intimate attachment between the cervix and the placenta; placental attachment to the cervix located below the entry point of the uterine vessel or below the anterior and posterior peritoneal reflection of the uterine surface, and inexistent fetal elements in the corpus uteri. The frequency of this type of ectopic pregnancy ranges between 1:1500 and 1:18,000 (3-6). On the other hand, Samal quotes a report by Celik of a frequency of 1:95,000 (7), accounting for 0.1% of all pregnancies, and being the least frequent of all ectopic pregnancies (8).

Given that it is an infrequent event, there are no studies demonstrating precise associations with risk factors; however, *in vitro* fertilization, inflammatory pelvic disease and endometrial curettage have been associated, although the evidence is controversial (9).

At present, cervical ectopic pregnancy diagnosis is more accurate due to the availability of quantitative measurements of serum human chorionic

gonadotropin (hCG), transvaginal ultrasound scans and magnetic resonance imaging (10). The most widely used ultrasound criteria are those described by Ushakov *et al.* (4), who proposes the following major criteria: a) endocervical localization of a gestational sac or trophoblast mass; b) closed internal os; and c) local trophoblast invasion of the endocervical tissue; and additional signs such as, d) visualization of embryonic or fetal structures in the ectopic gestational sac and presence of fetal heart rate, e) empty uterine cavity, f) endometrial decidualization, g) hourglass uterus, and h) presence of endocervical peritrophoblastic arterial flow on color Doppler. However, false positive results occur due to miscarriages picked up during passage through the cervix (9).

Historically, cervical ectopic pregnancies were diagnosed intraoperatively during dilation and curettage (D&C) due to the presence of profuse life-threatening bleeding, where the treatment was hysterectomy (11). However, starting in the 1980s (12) and with the advent of the diagnostic tools mentioned above that allowed early detection of this condition, there has been a significant shift in this approach and more conservative treatment modalities are in use currently, based on medical treatment with methotrexate (MTX) (systemic or local), endocervical Foley catheter balloon tamponade, D&C plus local prostaglandin injection, cervical cerclage and endocervical vasopressor injections, laparoscopy-assisted uterine artery ligation combined with hysteroscopic endocervical resection, hysteroscopic resection combined with uterine artery embolizations (UAE), with the aim of uterus and fertility preservation (4, 9, 13). Ushakov *et al.* described the conditions for initiating conservative treatment, including the following: having a reliable diagnosis of cervical ectopic pregnancy; a hemodynamically stable patient with mild or no bleeding; gestational age of less than 10 weeks based on last menstruation period; normal platelet count; normal liver and renal function (4). The choice of single or multiple-dose MTX regimens is dependent on pa-

tient condition. Quoting Hung, Murji describes the criteria for the use of multiple-dose MTX:  $\beta$ -hCG > 10,000 mIU/ml, gestational age of more than 9 weeks, presence of embryonic or fetal heart activity; and a crown-rump length of more than 10 mm on transvaginal ultrasound (14). When embryonic or fetal cardiac activity is present, the use of intrasac injections of potassium chloride (KCl) or MTX is recommended (15-17).

Successful medical treatment is defined as uterus preservation with MTX, even if a minor procedure is still required such as D&C, angioembolization or hysteroscopy; on the other hand, failed medical treatment is deemed to occur when the patient needs to be taken to hysterectomy or, even if the uterus is preserved, when a major procedure such as laparotomy, uterine artery ligation or hysterotomy is required (15).

Therefore, conservative treatment is the current standard of care in CP; however, this is a serious life-threatening condition, particularly in cases in which it has not been diagnosed early and, consequently, emergency general practitioners and obstetricians must keep this diagnostic possibility in mind, especially in the presence of massive genital bleeding. This also applies to primary care physicians providing prenatal care, in order to make conservative treatment possible following early diagnosis. Since Ushakov's pivotal review of the literature in 1997, there has been a paucity of information on the current management of this condition and its complications (4). We present the case of a patient with cervical ectopic pregnancy with the aim of conducting a review of the literature published since the year 2000 regarding treatment and complications of this condition.

## CASE PRESENTATION

A 30-year-old woman with moderate, painless, genital bleeding that had started three hours before. The woman presented to the Nariño Department University Hospital, a referral institution that serves patients of the state-subsidized regime under

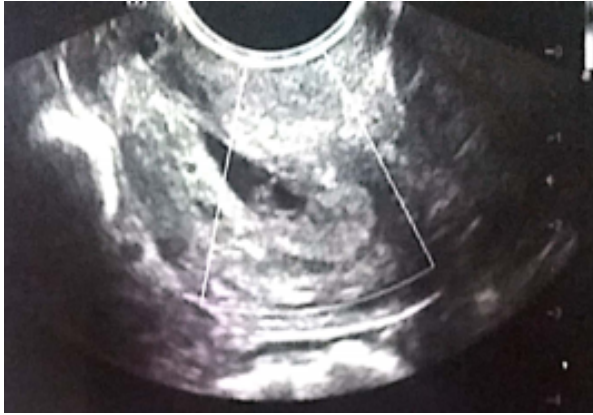
the General Social Security System in Colombia, located in the city of Pasto, in the southwestern region of Colombia. The patient reported 5 weeks of amenorrhea and brought a positive pregnancy test performed in a different institution. She had a previous history of cesarean section 7 years before and a family history of diabetes mellitus. The findings on clinical examination were: blood pressure 118/74 mm/Hg; heart rate 90 beats per minute; respiratory rate 18 breaths per minute; arterial oxygen saturation 96% with 21% fraction of inspired oxygen; no signs of peritoneal irritation; and bleeding on gynecological examination. Complete blood count report: hematocrit 41.4%; hemoglobin 14.1 g/dl; leukocytes 9800, neutrophils 60%; and human chorionic gonadotropin beta subunit ( $\beta$ -hCG) titre 4158 mg/dl. Transvaginal ultrasound findings were suggestive of early pregnancy with no evidence of a gestational sac, leading to the diagnostic impression of threatened miscarriage and a differential diagnosis of ectopic pregnancy. The patient was discharged with an order for a new  $\beta$ -hCG and recommendations regarding signs of alarm. On follow-up four days later, the patient returned with genital bleeding, a new  $\beta$ -hCG result of 16,189 mIU/ml and transvaginal ultrasound describing a single gestational sac at the level of the uterine endocervix, with adequate decidual reaction, below the insertion of the uterine arteries and the internal cervical os, closed appearance (Figure 1), no interruption of endometrial-cervical line continuity, and absence of the “sliding sign”. A new transvaginal ultrasound was performed two days later, showing persistence of the sac at the cervical level, a single embryo, positive embryocardia, which met Ushakov’s ultrasound criteria (4), thus confirming cervical ectopic pregnancy.

The patient expressed her wish of retaining fertility, prompting the decision of initiating conservative management after explaining the possibility of eventually needing surgical management in case of hemodynamic instability. Management was initiated with a single dose of methotrexate 60 mg IV which

was repeated later on days 3, 5 and 7 in association with 15 mg of oral calcium folinate on treatment days 4, 6 and 8. On treatment day 5,  $\beta$ -hCG values had doubled (35,199 mIU/ml). Pelvic magnetic resonance imaging (MRI) showed an image of cystic appearance with decidual reaction consistent with a cervical ectopic pregnancy and trophoblastic invasion of the anterior cervical stroma, sparing the wall of the bladder (Figure 2). The decision made in the medical-surgical meeting was to carry out obstetric D&C three hours after the administration of misoprostol and tranexamic acid.

On gynecological examination and speculscopy performed in the operating room, a gestational sac was observed through the external os. Tenaculum forceps were used to grasp the anterior lip of the cervix and the gestational sac was extracted with the help of Winter-Nasauer forceps. Then, D&C of the cervix and the uterine cavity was performed using a sharp curette, with no ensuing significant bleeding through the cervix. Finally, a Foley catheter with the balloon inflated with 15 cc of saline solution was placed in the endocervical canal in order to apply pressure and prevent bleeding from the bed of the intervention site. After the procedure, due to the high risk of hemodynamic decline, the patient was transferred preventatively to the intensive care unit for close monitoring of uterine bleeding. The surgical specimen was sent to the pathology laboratory.

Twenty-four hours into the postoperative period, the pressure of the Foley balloon was progressively diminished; there was no new uterine bleeding and hematocrit and hemoglobin values remained stable. Two days after the procedure,  $\beta$ -hCG levels dropped to 5282 mIU/ml and, by postoperative day 4, they were down to 1823 mIU/ml. The patient was discharged five days after the D&C procedure and on day 6 the  $\beta$ -hCG value was at 809 mIU/ml. Seventeen days after the procedure, the  $\beta$ -hCG value was at 16 mIU/ml. The histopathology result was reported as collapsed gestational sac with non-inflamed embryonic tissue and immature chorionic villi. Hysteroscopy performed three months



**Figure 1.** Transvaginal pelvic ultrasound.

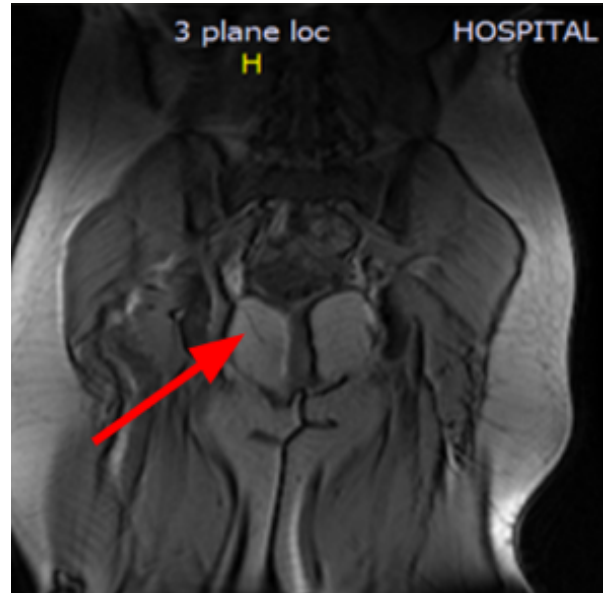
An irregular single gestational sac is observed at the level of the endocervix (distal to the internal os) with swelling loss and distal elongation, measuring 18 x 7 mm, with a 3 mm yolk sac seen in the inside. The image is consistent with a 5-week, 6-day cervical ectopic pregnancy.

later revealed normal uterine cavity and ostium, normal cervical canal and lesion-free internal os, confirming successful conservative medical-surgical management with uterine preservation and a satisfactory clinical course.

*Ethical considerations.* The patient signed the informed consent, authorizing the authors to publish the case.

## MATERIALS AND METHODS

A search for articles was conducted in Medline via PubMed, the SciElo online library, LILACS, and Google Scholar using the terms “cervical ectopic pregnancy,” “conservative treatment,” “curettage,” “methotrexate,” “uterine artery embolization,” “hysteroscopy,” with their corresponding terms in Spanish, as well as a snowball search using the studies identified as starting point. The selection included case reports and case series of patients with cervical ectopic pregnancy of any gestational age identified on ultrasound, who had received medical treatment with methotrexate, conservative surgical management with dilation and curettage, hysteroscopic management or uterine artery embolization (UAE), published in English and Span-



**Figure 2.** Pelvic magnetic resonance image.

High signal intensity rounded image localized in the cervix, with the longest diameters measuring 22 x 20 mm, hypointense rounded halo with peripheral ring enhancement in the contrast phase, consistent with cervical ectopic pregnancy.

ish between 2000 and 2019 for which the full text was available. The following aspects of the studies were assessed: design, type of medical/surgical treatment, country where the case was managed, and weeks of gestation at the time of diagnosis; for medical treatment, medications used, dose and route of administration were considered and for surgical treatment the aspects considered were surgical technique, complications, maternal outcome (success or failure), follow-up time and need for medical-surgical treatment.

## RESULTS

The search of the literature yielded 130 titles. Of these, 22 studies corresponding to case series and case reports that met the inclusion criteria were identified: 3 were described as prospective studies (18-20), 6 were retrospective studies (5, 14, 21-24), 3 were case series (25-27), and 10 were case reports (7, 16, 28-35). Overall, 15 studies assessed medical treatment (5, 7, 14, 18, 21-23, 25, 28-33, 35) and 9

assessed surgical treatment (7, 16, 19, 20, 24, 26, 27, 34, 35).

The selected texts were publications of groups from various countries such as Taiwan (20), India (7, 35), Greece (18), Canada (5, 14, 31), Turkey (22), Italy (16, 19), Cyprus (26), Egypt (26), United States (23, 25, 34), China (24), South Korea (27), Spain (33), Mexico (29), Venezuela (30), Cuba (32) and Colombia (28).

### Medical treatment

*Medications used.* Methotrexate (MTX) was the mainstay of management as initial approach in the studies described below (Table 1).

In a retrospective study, Vela *et al.* (5) reported 12 patients with cervical pregnancy of gestational age ranging between 6.5 and 9.1 weeks, 5 of whom were treated with MTX. In four cases, the initial management consisted of a single dose of MTX, and one case received local and intramuscular (IM) MTX. One patient exhibited adequate response to the single MTX dose, while the other 4 required additional treatment with a second dose of MTX (1 patient), uterine artery embolization (2 patients), curettage and vascular ligation (1 patient). The remaining patient, with a simultaneous intrauterine pregnancy, was treated with MTX and UAE resulting in the expulsion of both gestational sacs with no need for additional interventions. All cases were followed up for at least one year and conservative management was successful in all of them.

Kirk *et al.* (21) reported on a retrospective study of 7 patients with cervical pregnancy of 7-12 weeks of gestational age, 6 of whom received MTX while one was managed with a watch-and-wait approach. In this study, the use of single-dose MTX was indicated for cervical pregnancies without fetal cardiac activity, while for pregnancies with fetal cardiac activity, the use of the single-dose or multiple dose protocol with folinic acid or intra-amniotic MTX rescue was indicated. Three patients received a single dose, one patient received multiple doses, and 1 patient received oral and intra-amniotic doses

with successful results. One case required the use of complementary intra-amniotic KCl. Mean follow-up was 63 days.

Uludag *et al.* (22) reviewed ten patients between 23 and 40 years of age with CP of gestational age ranging between 6.2 and 8.2 weeks. Of them, 6 patients received multiple doses of systemic MTX and 4 received local intra-amniotic MTX injection. Management was considered successful in all ten cases, with a mean  $\beta$ -hCG remission of  $8.8 \pm 3.6$  weeks and a mean time for disappearance of the cervical mass on ultrasound of  $12.9 \pm 6.9$  weeks. Two patients developed complications: severe oral ulceration and increased  $\beta$ -hCG titres in one patient, requiring a switch to local MTX treatment; severe vaginal bleeding one week after local injection in a second patient, requiring transfusion of two units of red blood cells, curettage and tamponade with No. 18 Foley catheter balloon inflated with 30 ml, which resulted in adequate control of bleeding.

Martinez *et al.* (28) published the case report of a hemodynamically stable 37-year-old patient with early cervical ectopic pregnancy in whom MTX treatment was successful and uncomplicated.

De la loza Cava *et al.* (29) reported one case of a 14-week CP initially managed with a single intramuscular dose of MTX. Hemodynamic deterioration of the patient led to hysterectomy. The postoperative course was positive, with no clinical complications. Conservative management with MTX was considered to have failed.

Figuroa-Solano *et al.* (30) documented the case of a 37-year-old patient with a cervico-isthmic pregnancy. The treatment choice was multiple doses of MTX IV for 4 weeks. The patient went into hemodynamic decline and total abdominal hysterectomy was required, with no ensuing complications, confirming failed conservative management. The patient was discharged after 39 days with a pathology report of cervico-isthmic pregnancy and placenta increta.

Weibel *et al.* (31), in Canada, published two clini-

**Table 1.**  
**Conservative medical treatment: MTX in patients with cervical ectopic pregnancy.**  
**Review of the literature, 2000-2019**

Author	Year	Country	Study Design	Total patients	Patients meeting inclusion criteria	Gestational age	Intervention	Follow-up	Outcome
Vela G, <i>et al.</i> (5)	2007	Canada	Retrospective	12	5	1.6.5 weeks 2.6.6 weeks 3.8.8 weeks 4.8.8 weeks 5.9.1 weeks	4 patients: single dose of MTX 50 mg/m <sup>2</sup> IM 1 patient: MTX local and IM	1 year	Successful
Kirk, <i>et al.</i> (21)	2006	England	Retrospective	7	6	1.6 weeks 2.6 weeks 3.6 weeks 4.7 weeks 5.11 weeks 6.11 weeks	3 patients: single dose of MTX 50 mg/m <sup>2</sup> IM; 1 patient: multiple doses of MTX 1 mg/kg IM on days 1,3,5 plus rescue with folinic acid 0.1 mg/kg on days 2,4,6, 1 patient: intra-amniotic MTX; 1 patient: multiple doses of MTX IM plus intra-amniotic potassium chloride 5 mmol/L	Average of 63 days (range 34-139)	Successful
Uludag, <i>et al.</i> (22)	2017	Turkey	Retrospective	10	10	1.6.2 weeks 2.6.4 weeks 3.6.5 weeks 4.6.6 weeks 5.6.2 weeks 6.6.5 weeks 7.7.0 weeks 8. 6.3 weeks 9. 7.5 weeks 10. 8.2 weeks	6 patients: multiple doses of systemic MTX 1 mg/kg, alternating with 0.1 mg/kg of leucovorin IM (1 required change to local MTX treatment), 4 patients: local intra-amniotic injection of MTX 50 mg	Average of 12 weeks	Successful
Martínez <i>et al.</i> (28)	2017	Colombia	Case report	1	1	Unknown	Multiple doses of systemic MTX 1 mg/kg plus folinic acid	2 months	Successful
De la Loza Cava, <i>et al.</i> (29)	2012	Mexico	Case report	1	1	14 weeks	Single dose MTX 50 mg IM	3 days	Hysterectomy
Figueroa Solano, <i>et al.</i> (30)	2012	Venezuela	Case report	1	1	Unknown	Multiple doses of MTX IV	39 days	Hysterectomy
Weibel, <i>et al.</i> (31)	2012	Canada	Case report	2	2	1.5.6 weeks 2.7.4 weeks	Multiple doses of MTX 50 mg/m <sup>2</sup> IM 4 days plus oral folinic acid 5 mg/day	2 months	Successful

Continuation Table 1

Author	Year	Country	Study Design	Total patients	Patients meeting inclusion criteria	Gestational age	Intervention	Follow-up	Outcome
Mesogitis, <i>et al.</i> (18)	2005	Greece	Prospective	9	9	1.6 weeks 2.7.1 weeks 3.6.5 weeks 4.6.2 weeks 5.7.3 weeks 6.6.6 weeks 7.7.5 weeks 8.6.5 weeks 9.6.3 weeks	7 patients: single dose intra-amniotic MTX 25 mg; 2 patients: 2 doses of intra-amniotic MTX 25 mg.	22 to 72 days	Successful
Verma, <i>et al.</i> (23)	2009	United State	Retrospective	24	19	Mean gestational age 7.6 weeks (5-15 weeks)	MTX 50-75 mg/m <sup>2</sup> IM	Unknown	Successful
Murji, <i>et al.</i> (15)	2015	Canada	Retrospective	27	19	Mean gestational age: 27 weeks	13 patients: MTX single dose 50 mg/m <sup>2</sup> IM, 14 patients: MTX multiple doses 1 mg/kg IM on days 1,3,5,7 and leucovorin on days 2,4,6,8	2 to 13 days	Successful
Martinez Camilo, <i>et al.</i> (32)	2000	Cuba	Case report	1	1	8 weeks	MTX 50 mg IV for 4 days, alternating with folic acid 5 mg PO every 12 hours	Unknown	Successful
Samal, <i>et al.</i> (35)	2015	India	Case report	1	1	6.6 weeks	MTX multiple doses followed by D&C.	4 weeks	Successful
Samal, <i>et al.</i> (7)	2015	India	Case series	3	1	7 weeks	MTX multiple doses of 1 mg/kg IM on days 1,3,5,7 alternating with leucovorin at a dose of 0.1 mg/kg, plus intra-amniotic potassium chloride injection	5 weeks	Successful
Taylor, <i>et al.</i> (25)	2011	United States	Case series	4	1	1.7 weeks 2.6 weeks 3.7 weeks 4.7 weeks	MTX single dose 50 mg/m <sup>2</sup> IM	3-4 weeks	Successful
Tejero, <i>et al.</i> (33)	2010	Spain	Case report	1	1	7 weeks	Intra-sac MTX 50 mg plus MTX 96 mg IM	4 months	Successful



**Table 2.**  
**Surgical treatment with dilation and curettage, hysteroscopy, uterine artery ligation or embolization in patients with cervical ectopic pregnancy. Review of the literature, 2000-2019**

Conservative surgical management									
Dilation and curettage									
Author	Year	Country	Study Design	Total patients	Patients meeting inclusion criteria	Gestational age	Intervention	Follow-up	Outcome
De la Vega, <i>et al.</i> (34)	2007	United States	Case report	1	1	7 weeks	D&C plus boprost and balloon tamponade	7 days	Successful
Samal, <i>et al.</i> (7)	2015	India	Case series	3	1	8 weeks	D&C plus balloon tamponade followed by MTX 50 mg IM	2 months	Successful
Hysteroscopy									
Author	Year	Country	Study Design	Total patients	Patients meeting inclusion criteria	Gestational age	Intervention	Follow-up	Outcome
Mangino, <i>et al.</i> (16)	2014	Italy	Case report	1	1	6 weeks	Intra-amniotic MTX, two doses of systemic MTX and rescue hysteroscopic resection due to failed response to MTX	2 months	Successful
Scutiero, <i>et al.</i> (19)	2013	Italy	Prospective	5	5	6 weeks 9 weeks 6 weeks 7 weeks 8 weeks	Bilateral uterine artery embolization followed by hysteroscopic cervical ectopic pregnancy excision	15 days	Successful
Tanos, <i>et al.</i> (26)	2019	Cyprus/ Egypt	Case series	4	4	7 weeks 6 weeks 6 weeks 5 weeks 4 days	Hysteroscopy	1 day	Successful

Continuation Table 2

Author	Year	Country	Study Design	Total patients	Patients meeting inclusion criteria	Gestational age	Intervention	Follow-up	Outcome
<b>Hysteroscopy</b>									
Kim, <i>et al.</i> (27)	2008	South Korea	Case series	10	10	< 4 weeks < 5 weeks 6 weeks 5 weeks 6 days 6 weeks 2 days < 5 weeks < 5 weeks 5 weeks 6 days < 4 weeks 6 weeks	Hysteroscopy	28 days	Successful
<b>Uterine artery ligation or embolization</b>									
Author	Year	Country	Study Design	Total patients	Patients meeting inclusion criteria	Gestational age	Intervention	Follow-up	Outcome
Kung, <i>et al.</i> (20)	2004	Taiwan	Prospective	27	6	9 weeks 9 weeks 6 weeks 6 weeks 6 weeks.	Laparoscopic uterine artery ligation	35-90 days	Successful
Hu, <i>et al.</i> (24)	2016	China	Prospective	19	19	Between 5.1 and 11 weeks of gestation	Uterine artery embolization followed by curettage	59 months in average	Successful

cal cases of patients with EP of 5.6 and 7.4 weeks of gestation managed conservatively with multiple doses of systemic MTX alternating with oral folinic acid, resulting in adequate clinical response and no need for additional interventions, confirming successful conservative management.

Mesogitis *et al.* (18) conducted a prospective study of 9 patients with EP of gestational ages ranging between 5.4 and 13.7 weeks treated conservatively with intra-amniotic MTX; 2 patients with positive embryocardia on a follow-up ultrasound received a second dose of intra-amniotic MTX. After two additional ultrasound scans showing evidence of fetal demise, cervical curettage was performed. Treatment was successful in all patients and there was no need for transfusion or any other major procedure.

In a retrospective study by Verma *et al.* (23) of 25 patients with CP ranging between 5 and 15 weeks of gestation, 15 patients had live fetuses and a total of 19 received MTX IM. Treatment was successful in all of them, but 4 patients had acute bleeding, 1 needed both intravascular treatment and D&C plus blood product transfusion, another patient had chronic bleeding requiring transfusion, and one more patient had retained fetal elements requiring D&C. None of the patients required hysterectomy. It is not clear whether the complications occurred in the patients who received MTX.

Samal *et al.* (7) reported 3 cases of CP. One of the cases was a 26-year-old woman in whom a 7-week embryo with fetal heart rate was identified. She received an injection of KCl and MTX.  $\beta$ -hCG values were followed on a weekly basis and had become negative by 5 weeks; the treatment was considered successful.

Murji *et al.* (15) published a retrospective study of 27 patients with CP of a mean gestational age of 5 weeks, all of whom received systemic intramuscular MTX either in a single or multiple dose protocol. Intra-amniotic KCl was used in 19 patients with positive fetal heart rate. Seven patients underwent

UAE: in 2, the procedure was performed to prevent bleeding, in 2 it was used for the management of severe bleeding, and in 3 in combination with D&C. Management was deemed successful in all of the patients.

Martínez *et al.* (32), in Cuba, documented one case of CP of approximately 8 weeks, in which a multiple-dose regimen of MTX was used. On follow-up, ultrasound showed persistence of the ectopic pregnancy with genital bleeding, leading to the decision of performing curettage of the cervical canal as definitive treatment, with no ensuing complications.

Tejero *et al.* (33) reported a case in which intrasac and intramuscular MTX was used simultaneously. Follow-up ultrasound two weeks after the administration of the drug showed persistence of a gestational sac containing an embryo with no heart beat at the level of the cervix. The patient was taken to obstetric curettage, with no complications.

In a series of 4 cases of CP, Taylor *et al.* (25) used MTX IM as initial treatment, with adequate clinical response in 3 patients; the fourth patient underwent UAE before D&C. The clinical course in all 4 cases was adequate and conservative treatment was considered successful.

Samal *et al.* (35) reported the case of a 29-year-old patient with CP and a live embryo of 6 weeks and 6 days of gestational age documented on ultrasound. Management was initiated with intrasac administration of KCl and a regimen of multiple-doses of MTX IM (1 mg/kg), alternating with leucovorin (0.1 mg/kg). On day 4,  $\beta$ -hCG was 87,958 mIU/ml, and ultrasound revealed an endocervical mass 4.2 x 3.4 x 3.4 cm in size. After four doses of MTX and leucovorin,  $\beta$ -hCG dropped to 42,955 mIU/ml with no changes in size seen on ultrasound imaging of the endocervix. The patient was discharged and was followed on a weekly basis with  $\beta$ -hCG and transvaginal ultrasound. Two weeks later,  $\beta$ -hCG was 1267 mIU/ml but the ultrasound image persisted. This prompted admission for D&C,

which proceeded uneventfully. Four weeks after the procedure,  $\beta$ -hCG was negative and no evidence of endocervical collection was seen on ultrasound. Management was considered successful.

Overall, 95 patients with CP treated with MTX were identified. The most frequent complication was bleeding in 11 cases (12%); complementary treatment was required in 25 patients (26%), the most frequent being D&C (8 cases) and UAE (10 cases) which was performed prophylactically in 7 cases before D&C and treatment with MTX. In two cases, one of which was a cervico-isthmic pregnancy, abdominal hysterectomy was required.

### Conservative surgical treatment

*Endocervical dilation and curettage:* No studies in which D&C was used as the only treatment were found; there were two cases in which D&C plus Foley catheter balloon tamponade was used. De la Vega *et al.* (34) documented one 7-week cervical pregnancy with conservative surgical management: under general anesthesia, the patient received an infiltration of 250 micrograms ( $\mu$ g) of carboprost for vasoconstriction; following cervical cerclage, a curette was advanced to the external os under abdominal ultrasound guidance, retrieving a large volume of cervical gestation products from the inside of the cervix. After this procedure, a 30 ml Foley catheter balloon inflated with 25 ml of saline solution was placed in the cervical canal. There were no intra- or postoperative complications and the balloon was removed 2 days later. Successful conservative surgical treatment was confirmed during follow-up.

Samal *et al.* (7) reported one case treated with D&C in a 27-year-old primigravida with an 8-week CP. An endocervical uterine image 4 x 4 cm in size suggested a cervical ectopic pregnancy;  $\beta$ -hCG was 1047 mIU/ml. Endocervical curettage was followed by the placement of a No. 18 Foley catheter balloon inflated with 40 ml of saline solution, achieving hemostasis, although the patient needed 3 units of red blood cells and 1 unit of fresh frozen plasma. The

balloon was removed uneventfully after 24 hours, the patient received one dose of MTX 50 mg IM, and was discharged on day 3. The pathology report described chorionic villi, decidual tissue and glands, plus cervical stroma, confirming the diagnosis. The patient was followed on a weekly basis with  $\beta$ -hCG and, 2 months after the procedure, the diagnosis was negative and the treatment was considered successful (Table 2).

*Hysteroscopy:* Manguino *et al.* (16) reported one case of a 40-year-old patient with a history of inflammatory pelvic disease and in vitro fertilization with embryo transfer resulting in conception. She presented with cervical ectopic pregnancy and six weeks of amenorrhea. The patient received one amniotic intrasac injection of MTX under ultrasound guidance plus systemic doses; poor response was poor and a rise of  $\beta$ -hCG from 1100 mIU/ml to 4274 mIU/ml led to the decision of performing hysteroscopic resection with no other additional intervention. The treatment was considered successful and there were no complications.

Scutiero *et al.* (19) assessed 5 patients with CP between 6 and 9 weeks of gestation. Embryonic cardiac activity was present in all cases, and  $\beta$ -hCG ranged between 15,482 and 74,684 mIU/ml. Management was based on combined uterine artery embolization and hysteroscopic resection. In all cases, length of stay was 4 days and outcomes were successful.

Tanos *et al.* (26) presented 4 patients with CP of 5 to 7 weeks of gestation and  $\beta$ -hCG between 930 and 13,790 mIU/ml. They all underwent hysteroscopic management alone, using vasopressors as adjuncts (diluted adrenalin 1:40/2 cm and diluted vasopressin 1:20/3.5 ml infiltration 5-7 mm in three parts adjacent to the ectopic implantation site). The result was successful in all patients. Hospital length of stay varied between 8 and 24 hours, and all patients were discharged with no complications. These authors presented a review of the literature that included 16 publications of CP treated with surgical hysteroscopy.

Kim *et al.* (27), in 10 hemodynamically stable patients, assessed the combined use of hysteroscopic resection with H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) infusion and intracervical vasopressin injection (0.2 U – 15 ml, applied at 3, 6, 9 and 12 o'clock); they used hydrogen peroxide based on the premise that it induces cell death due to oxygen toxicity. The 10 patients were between gestation weeks 4 and 6 and had  $\beta$ -hCG levels ranging between 1561 and 47,629 mUI/ml; none of them received MTX. All the interventions were successful and  $\beta$ -hCG was negative in all patients after 4 weeks of follow-up.

Overall, 20 patients managed with hysteroscopy were identified: in 14, additional management with vasopressin was used, after the use of MTX in 1 patient, and in UAE in 5. Hysteroscopy was successful in all cases (Table 2).

*Uterine artery embolization or ligation:* Kung *et al.* (20) describe 6 patients with CP taken to conservative surgical management consisting of laparoscopic uterine artery ligation under general anesthesia. After identifying the vascular structures, the surgeons proceeded to ligate the distal portion using 1-0 vicryl suture until uterine and cervical blood flow was blocked. Hysteroscopy was performed following the laparoscopic procedure in order to localize the cervical gestational sac for resection. In all cases, blood loss was minimal and there were no serious complications requiring hysterectomy. Mean time until return of menses in these patients was 63 days.

Hu *et al.* (24), in a retrospective study of 19 patients with cervical pregnancy, performed UAE followed by curettage between 24 and 72 hours after the endovascular procedure. None of the 19 patients developed vaginal bleeding or other procedure-related complications during the postoperative period. The uterus was preserved in 100% of the cases.

## CONCLUSIONS

MTX treatment continues to be the conservative treatment most frequently described in the international literature. Dilatation and curettage with endocervical balloon tamponade may be an emergency

management option for CP in primary healthcare centers. In facilities equipped with high complexity technology, options like uterine artery embolization before surgical procedures and hysteroscopy must be considered. Considering that early diagnosis of CP is now possible, multi-center studies comparing the different management options to determine their safety and effectiveness are required.

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## AUTHOR CONTRIBUTIONS

Henry Hernán-Bolaños participated in the planning of the article and review of the content in the final manuscript. Andrés Ricaurte-Sossa participated in the medical meeting in which the decision was made to initiate conservative management in the patient, and in collecting the data from the selected studies.

Fabio Zarama-Márquez participated in the medical meeting in which the decision was made to initiate conservative management in the patient, in the analysis and selection of the literature, and drafting of the manuscript. Ruth Fajardo-Rivera participated in patient care, review of the data and information, and drafting of the manuscript. Ruben Chicaiza participated in the planning of the article and its structure, verification of information quality, and reference documentation.

Carlos Andrés Guerrero-Mejía participated in the search for diagnostic imaging, laboratory data and image descriptions, and in the review of the manuscript.

Andrés Ricaurte-Fajardo participated in data collection from the literature and review of the manuscript.

**Conflict of interest:** none declared.