ORIGINAL BRIEF

1. Centro Ginecológico y Ecográfico Dra. Úrsula Guerrero, Chiclayo, Perú
a. Specialist in Gynecology and Obstetrics, subspecialty in Fetal Medicine and Fetal Surgery. ORCID: 0009-0003-1629-9529

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Corresponding author:
Dr. Úrsula Janneth Guerrero Leonardo.
☎ 988574525.
✉ ursulitag4@gmail.com

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Outpatient management of uncomplicated ectopic pregnancy with oral methotrexate

Manejo ambulatorio del embarazo ectópico no complicado con metotrexato oral

Guerrero-Leonardo Úrsula Janneth[1a]

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ABSTRACT

Background. Ectopic pregnancy is a significant cause of maternal morbidity in the first trimester. Although intramuscular methotrexate is the standard medical treatment, the oral route has emerged as an alternative in outpatient settings with logistical limitations. Objective. To describe the experience in the outpatient management of uncomplicated ectopic pregnancy with oral methotrexate in a gynecological center. Materials and methods. Observational, descriptive, and retrospective study. Ten patients were included, all treated with oral methotrexate (1 mg/kg every 8 hours for two days). Results. The mean age was 27.8 years (range 21–35). All patients met the criteria for early response (>15% decrease on day 4 and <50 mIU/mL on day 7) and achieved complete β-hCG negativization during follow-up, without adverse events or need for additional doses or surgery. Conclusions. Outpatient use of oral methotrexate was effective and safe in selected patients.

Keywords: Ectopic pregnancy; methotrexate; ambulatory care; oral administration.

RESUMEN

Antecedentes. El embarazo ectópico es una causa importante de morbilidad materna en el primer trimestre. Aunque el metotrexato intramuscular es el tratamiento médico estándar, la vía oral ha surgido como alternativa en contextos ambulatorios con limitaciones logísticas. Objetivo. Describir la experiencia en el tratamiento ambulatorio de embarazo ectópico no complicado con metotrexato oral en un centro ginecológico. Materiales y métodos. Estudio observacional, descriptivo y retrospectivo. Se incluyeron 10 pacientes, tratadas con metotrexato oral (1 mg/kg cada 8 horas por dos días). Resultados. La edad media fue de 27,8 años (rango 21–35). Todas las pacientes cumplieron los criterios de respuesta temprana (disminución >15% al día 4 y niveles <50 mIU/mL al día 7) y alcanzaron negativización completa de β-hCG durante el seguimiento, sin eventos adversos ni necesidad de dosis adicionales o cirugía. Conclusiones. El uso ambulatorio de metotrexato oral fue efectivo y seguro en pacientes seleccionadas.

Palabras clave: Embarazo ectópico, metotrexato, atención ambulatoria, administración Oral.

Abstract

Ectopic pregnancy is a major cause of maternal morbidity and mortality in the first trimester. It is estimated that between 5% and 10% of all pregnancy-related maternal deaths are attributable to ectopic pregnancies, with a rupture rate of up to 15% in Western countries and a prevalence of up to 18% among women who seek emergency care for abdominal pain and bleeding during the first trimester[(1)].

Globally, between 1990 and 2019, more than 66,000 new cases of ectopic pregnancy were reported per year, with a general downward trend in the age-standardized rate, with an estimated annual percentage change (EAPC) of −1.14%; However, the burden persists in regions with low socioeconomic development[(2)].

An uncomplicated ectopic pregnancy is defined as one without signs of rupture, without free fluid in the pelvic cavity, without embryonic cardiac activity, and in hemodynamically stable patients. In these cases, medical treatment with methotrexate has been established as an effective option. Although the parenteral (intramuscular) route is the most commonly used, recent studies have reported the viability of oral methotrexate

in selected contexts, with comparable success rates and lower logistical requirements[3,4]. Some initial studies, such as those by Lipscomb et al. and Korhonen et al., have documented encouraging results regarding its efficacy and safety[3,4], although published clinical experience is still limited, especially in Latin America.

In Peru, the Clinical Practice Guidelines of the National Maternal and Perinatal Institute (2018) recognize the use of methotrexate as part of medical treatment in selected cases of uncomplicated ectopic pregnancy. However, it is indicated exclusively for intramuscular or local administration under ultrasound guidance, without yet considering oral administration as a therapeutic alternative[5].

In this context, the present study describes the results of a cohort of patients with uncomplicated ectopic pregnancy treated on an outpatient basis with oral methotrexate at a gynecological center in Chiclayo, Peru, during 2023. The aim is to provide local evidence on the feasibility and safety of this therapeutic modality, which is particularly relevant in settings with limited resources and a high disease burden.

Methods

Design and setting: Observational, descriptive, retrospective study. The study was conducted at the Dr. Úrsula Guerrero Gynecology and Ultrasound Center in Chiclayo, Peru, between January and December 2023.

Participants: All patients with a confirmed diagnosis of uncomplicated ectopic pregnancy who were treated on an outpatient basis during the study period were included. According to the recommendations of the National Maternal Perinatal Institute of Peru (2018) and the guidelines of the Royal College of Obstetricians and Gynaecologists (2016), uncomplicated ectopic pregnancy was defined as one that simultaneously meets the following criteria: 1) clinical stability, 2) unruptured gestational mass ≤3.5 cm on transvaginal ultrasound with no embryonic cardiac activity or free fluid in the pelvic cavity, and 3) low or progressively declining serum β-hCG levels[5,6].

Patients who were breastfeeding, had renal, hepatic, or hematological dysfunction, active pulmonary disease, alcoholism, active peptic ulcer, or a gestational mass >3.5 cm were excluded. All patients had documented potential for outpatient follow-up.

Outcomes: The primary outcome was clinical resolution of ectopic pregnancy, defined as disappearance of symptoms and complete negativization of β-hCG (<5 mIU/mL). The following were evaluated as intermediate outcomes of early response: a) >15% decrease in β-hCG on the fourth day, and b) levels <50 mIU/mL on the seventh day after the start of treatment.

Variables studied: Data were collected on age, gestational age at diagnosis, location of pregnancy, ultrasound size of the gestational sac, history of ectopic pregnancy, decrease in β-hCG (>15% on day 4), levels <50 mIU/mL on day 7, adverse reactions to treatment, and need for surgical intervention.

Data analysis: Descriptive statistics were used. Qualitative variables were expressed as absolute frequencies and percentages; quantitative variables were expressed as means and ranges. The analysis was performed using IBM SPSS Statistics v18.0 software.

Ethical aspects: Informed consent was not requested as this was a retrospective study with anonymized data and minimal risk.

Results

Ten patients with a confirmed diagnosis of uncomplicated ectopic pregnancy were included, treated on an outpatient basis with oral methotrexate at a gynecological center in Chiclayo, Peru, between January and December 2023. The mean age was 27.8 years, with a range of 21 to 35 years.

Gestational age and clinical characteristics

One patient (10%) was diagnosed in week 5 of gestation, four (40%) in week 6, four (40%) in week 7, and one (10%) in week 8. No patient presented embryonic cardiac activity or free fluid in the pelvic cavity. Six cases (60%) were located in the right fallopian tube, three (30%) in the left fallopian tube, and one case (10%) in a cesarean

scar. The size of the gestational sac was between 20 and 35 mm in seven patients (70%) and less than 20 mm in three patients (30%). Two patients (20%) reported a history of ectopic pregnancy.

Clinical outcome and response to treatment

All patients received the split-dose outpatient regimen of oral methotrexate, with a total dose of approximately 50 mg over two days. On the fourth day, 100% had a >15% decrease in β-hCG levels, and on the seventh day, all had reached levels <50 mIU/mL. No patient experienced adverse events, required a second dose, or required surgical intervention.

Discussion

In this study, all women diagnosed with uncomplicated ectopic pregnancy treated on an outpatient basis with fractionated oral methotrexate (50 mg over two days) achieved a reduction of more than 15% in β-hCG on the fourth day and levels below 50 mIU/mL on the seventh day. None experienced adverse effects, required additional doses, or required surgical intervention. These results, which include the successful resolution of a case located in a cesarean scar, show that this therapeutic alternative could be safe and effective when patients are appropriately selected and close clinical and laboratory follow-up is ensured.

Table 1. Clinical characteristics and outcomes of patients.

Variable	Result
Mean age (range)	27.8 years (21–35)
Gestational age at diagnosis	
– 5 weeks	1/10 (10%)
– 6 weeks	4/10 (40%)
– 7 weeks	4/10 (40%)
– 8 weeks	1/10 (10%)
Ectopic pregnancy location	
– Right tubal	6/10 (60%)
– Left tubal	3/10 (30%)
– Cesarean section scar	1/10 (10%)
Gestational sac size	
– < 20 mm	3/10 (30%)
– 20–35 mm	7/10 (70%)
History of ectopic pregnancy	2/10 (20%)
Embryonic cardiac activity present	0/10 (0%)
Free fluid in pelvic cavity	0/10 (0%)
β-hCG decrease >15% by day 4	10/10 (100%)
β-hCG <50 mIU/mL by day 7	10/10 (100%)
Adverse reactions to treatment	0/10 (0%)
Need for second dose of methotrexate	0/10 (0%)
Need for surgery	0/10 (0%)

The medical treatment of ectopic pregnancy has evolved toward less invasive alternatives for selected patients, with intramuscular methotrexate being the standard option in most international clinical guidelines[1]. However, in regions with low healthcare coverage, oral administration has emerged as a viable strategy in settings with good access to ultrasound and laboratory follow-up.

From a pathophysiological point of view, ectopic pregnancy involves the implantation of the blastocyst outside the endometrial cavity, usually in the fallopian tubes, which carries a risk of hemorrhage if not managed promptly[7]. In uncomplicated cases with no signs of rupture, medical treatment with antimetabolite drugs such as methotrexate allows for progressive resolution of the trophoblastic tissue without the need for surgical intervention, thus reducing surgical risks, loss of tubal fertility, and hospital costs[8].

Most published reports on oral methotrexate date back more than two decades, reflecting the scarcity of recent research on this route of administration. Korhonen et al. (1996) conducted a randomized double-blind trial in 60 women, using oral methotrexate at 2.5 mg/day for five days (total dose 12.5 mg) versus placebo. Both groups achieved a success rate of 77%, with no significant differences in resolution time or the need for surgery. A more rapid decline in β-hCG was observed between days 5 and 12 in the treated group (p = 0.016), although without significant clinical impact[4].

Lipscomb et al. (2002) treated 22 patients with 60 mg/m² of oral methotrexate in two divided doses. Nineteen (86%) avoided surgery, with a mean remission time of 36.5 days (±18.7). Sixty-eight percent received a single cycle, while 32% required two or three cycles. Mild adverse effects were reported, such as abdominal pain (86%), nausea (18%), and abdominal distension (23%)[3].

Wildt et al. (1993) reported two cases treated with 10 mg orally (2 mg daily for five days), achieving complete remission in three weeks. One patient had a subsequent pregnancy and another had mild leukopenia (3000/mm³), with no liver or mucosal toxicity[9]. Chryssikopulos et al. (1989)

described three cases with laparoscopic diagnosis of ectopic pregnancy, treated with 140 mg of oral methotrexate in two cycles. All three patients had a significant drop in β-hCG (65%–75% in 9–12 days), but ultimately required minilaparotomy for definitive resolution. No complications were reported, and two patients achieved subsequent pregnancies[10].

In 1988, Patsner and Kenigsberg first reported the successful use of oral methotrexate without folinic acid rescue to treat a persistent ectopic pregnancy after conservative tubal surgery. The treatment, administered at a dose of 0.4 mg/kg/day for 5 days, succeeded in reducing β-hCG levels to negative without adverse effects, demonstrating for the first time the clinical viability of this route of administration in selected patients, even in the postoperative context[11].

These differences reflect not only variability in dosage, but also in inclusion criteria and follow-up protocols. The dose used in our study (50 mg divided over two days) falls between the low doses used by Korhonen (12.5 mg total) and the high doses used by Lipscomb (60 mg/m²), which could influence the rapid decline in β-hCG observed.

In our study, in addition to evidence in tubal pregnancies, a case of ectopic pregnancy in a cesarean scar was successfully treated. Other less frequent locations, such as cornual or interstitial ectopic pregnancy, have been treated with systemic methotrexate or ultrasound-guided local injection in selected and early-diagnosed cases, although these approaches were not the focus of the present study and are mentioned only for context[12–15].

Ectopic pregnancy continues to be a major cause of maternal morbidity and mortality in the first trimester, with a high incidence in less developed regions[16]. A global burden analysis between 1990 and 2019 estimated more than 66,000 new cases per year, with a higher concentration in areas with less access to surgical services or specialized medications[2]. In these settings, having effective oral treatment available may represent a relevant strategy from an operational and health perspective.

Among the limitations of the study is the small sample size, which prevents the results from being extrapolated to larger populations. In addition, although a drop in β-hCG to levels <50 mIU/mL was reported on day 7, the total time to complete negativity (<5 mIU/mL) was not recorded, which limits the comprehensive evaluation of the duration of treatment.

The results suggest that, in selected patients under close monitoring, oral methotrexate could be a safe and effective alternative, although the evidence is preliminary. Its use could be considered progressively in institutions with the capacity for close monitoring, while multicenter controlled studies are developed to define with greater certainty its efficacy, safety, and cost-effectiveness profile compared to conventional regimens.

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