Methotrexate for the treatment of unruptured tubal ectopic pregnancy

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CLINICIAN'S CAPSULE

What is known about the topic?
Methotrexate is widely accepted as first-line treatment of non-ruptured ectopic pregnancy and may be considered for women with a suspected ectopic pregnancy.

What did this study ask?
What are the outcomes of pregnant women with suspected ectopic pregnancy who received methotrexate as first-line treatment?

What did this study find?
Of patients treated with methotrexate, 18% went on to require surgical management, with 11.2% having ruptured on surgical evaluation.

Why does this study matter to clinicians?
Emergency department (ED) clinicians must be aware of the risk of methotrexate failure and have a high index of suspicion for patients returning to the ED.

ABSTRACT

Objective: The objective of this study was to determine the outcomes of women who presented to the emergency department (ED) with suspected ectopic pregnancy and received methotrexate as first-line treatment.

Methods: This was a retrospective chart review of pregnant (< 12 week' gestational age) women from an academic tertiary care ED with a diagnosis of ectopic pregnancy, rule-out ectopic pregnancy, or pregnancy of unknown location over a 7-year period.

Results: Of 612 patients with a suspected ectopic pregnancy at initial ED presentation, 326 (53.3%) had non-ectopic pregnancy outcomes, 30 (4.9%) were diagnosed with a ruptured ectopic pregnancy at the index ED visit, and 18 (2.9%) were diagnosed and managed as non-tubal ectopic pregnancies and excluded from further analyses; 238 patients were diagnosed with a tubal ectopic pregnancy, and 152 (63.9%) were treated with methotrexate at the index ED visit or in follow-up. Of patients treated with methotrexate, 27 (17.8%) went on to require surgical management, with 17 (11.2%) documented as having ruptured on surgical evaluation.

Conclusion: The proportion of patients failing methotrexate as first-line treatment was higher than previously reported. Further investigation is needed to determine whether methotrexate failure was due to non-adherence to recommended guidelines.

RÉSUMÉ

Objectif: L'étude visait à déterminer les résultats cliniques de l'administration de méthotrexate en traitement de première intention au service des urgences (SU), chez des femmes souffrant d'une grossesse ectopique présumée.

Méthode: Il s'agit d'un examen rétrospectif de dossiers de femmes enceintes (< 12 semaines de gestation), mené dans un SU d'un hôpital universitaire de soins tertiaires, chez qui a été posé un diagnostic de grossesse ectopique, a été écartée la possibilité de grossesse ectopique ou a été confirmée une grossesse mais de siège inconnu, et ce, sur une période de 7 ans.

Résultats: Sur 612 patientes chez qui un diagnostic de grossesse ectopique présumée a été posé au moment de la consultation initiale au SU, 326 (53,3 %) avaient une grossesse non ectopique, 30 (4,9 %) souffraient d'une rupture de grossesse ectopique au moment de la consultation de référence au SU et 18 (2,9 %) étaient porteuses d'une grossesse ectopique non tubaire et ont été traitées en conséquence, mais ces dernières ont été écartées du reste de l'étude; 238 patientes souffraient d'une grossesse ectopique tubaire et 152 (63,9 %) ont reçu du méthotrexate au moment de la consultation de référence au SU ou durant le suivi. Parmi les patientes traitées par le méthotrexate, 27 (17,8 %) ont dû être opérées et, sur ce nombre, 17 (11,2 %) souffraient d'une rupture de grossesse au moment de l'évaluation en cours de chirurgie.

Conclusion: La proportion de patientes chez qui le traitement de première intention par le méthotrexate a échoué était plus

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élevée que celle indiquée dans des données antérieures. Il faudrait donc mener d'autres recherches afin de déterminer si l'échec du traitement par le méthotrexate était attribuable au non-respect des lignes directrices recommandées.

Keywords: ectopic pregnancy, methotrexate, patient outcomes

INTRODUCTION

For patients presenting to the emergency department (ED) with first trimester bleeding or abdominal pain, 6%-16% will have an ectopic pregnancy.[1] Early detection of ectopic pregnancy and careful management are critical to prevent adverse clinical outcomes, including fallopian tube rupture, decreased future fertility, and death.[2] Methotrexate is widely accepted as first-line treatment of non-ruptured ectopic pregnancy and may be considered for women with a confirmed ectopic pregnancy who are hemodynamically stable with an unruptured mass.[3,4] In appropriately selected patients, the overall success rate for women treated with methotrexate for an ectopic pregnancy is 90%.[5] Relative contraindications to methotrexate use include pre-treatment beta-human chorionic gonadotropin (bHCG) levels higher than 5,000 mIU/mL, the presence of fetal cardiac activity (FCA), and ectopic pregnancy size $>$ 4 cm.[6,7] Failure of methotrexate therapy may result in tubal rupture; therefore, ED clinicians must be aware of the risk of methotrexate failure and have a high index of suspicion for patients returning to the ED.

The objective of this study was to determine the outcomes of pregnant women who presented to the ED with suspected ectopic pregnancy and received methotrexate as first-line treatment.

METHODS

This was a single-centre, retrospective medical record review of pregnant ($<$ 12 weeks' gestational age), adult ($\geq$ 18 years) women discharged from the ED of an academic tertiary care centre (annual ED census 60,000) in Toronto, Ontario, with a diagnosis of ectopic pregnancy, rule-out ectopic pregnancy, or pregnancy of unknown location over a 7-year period (January 2010 to January 2017). This institution has a high-acuity obstetrical care program and an early pregnancy clinic (EPC) that sees patients within 24-72 hours following ED discharge. The study protocol was approved by the institutional Research Ethics Board (17-0075-C).

Trained research personnel reviewed the medical records and extracted data using a computerized, data abstraction form. The primary outcome was the proportion of women who failed medical management with methotrexate after being discharged from the ED. Clinical features and pregnancy-related outcomes were also reported.

RESULTS

Of 612 patients with a suspected ectopic pregnancy at initial ED presentation, 326 (53.3%) had non-ectopic pregnancy outcomes, 30 (4.9%) were diagnosed with a ruptured ectopic pregnancy at the index ED visit, and 18 (2.9%) were diagnosed and managed as non-tubal ectopic pregnancies and excluded from further analyses. Treatments at the time of discharge from the index ED visit were as follows: 95 (39.9%) received methotrexate, 124 (52.1%) underwent expectant management, and 21 (8.0%) underwent surgical management. Only one patient received methotrexate without documented consultation by gynecology (Figure 1). After the index ED visit, 28 (11.8%) patients went on to have a ruptured ectopic pregnancy, 17 (60.7%) of whom were initially treated with methotrexate.

Of the 152 patients treated with methotrexate at the index ED visit or in follow-up, 27 (17.8%) went on to require surgical management with 17 (11.2%) documented as having ruptured on surgical evaluation, and 2 (1.3%) had unknown outcomes. Patients who failed methotrexate treatment were more likely to receive a second dose of methotrexate, have higher bHCG levels, have FCA on ultrasound, and more likely to return to the ED within 30 days.

Twenty (13.1%) patients had at least one relative contraindication for receiving methotrexate (pre-treatment bHCG levels higher than 5,000 mIU/mL, the presence of FCA, or ectopic pregnancy size $>$ 4 cm). Of these 20 patients, 5 (25.0%) had an ectopic rupture, 3 (15.0%) required non-urgent surgical management, and 12 (60.0%) were successfully medically managed. Of the 132 patients who received methotrexate without relative contraindications, 12 (9.1%) had an ectopic

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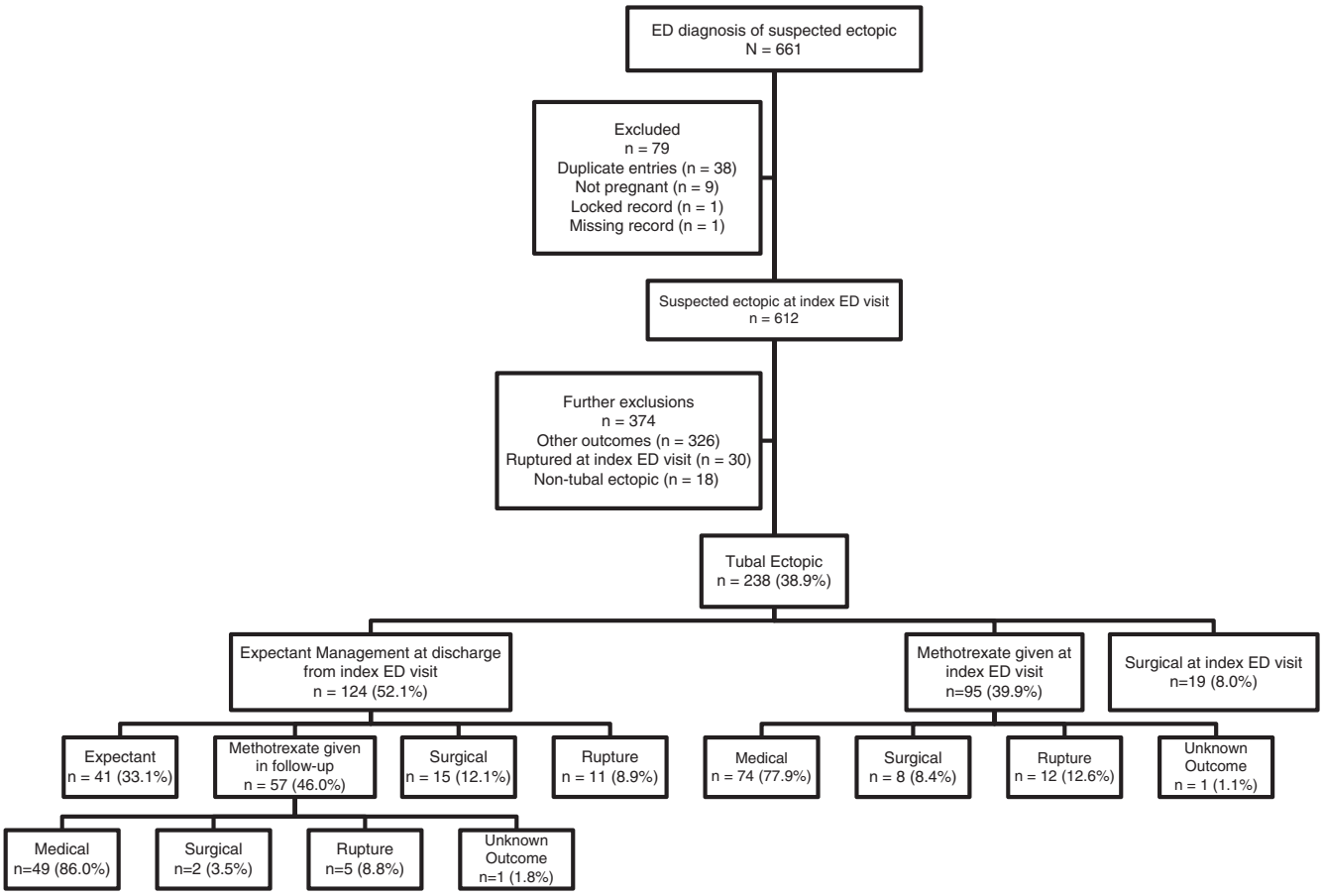

Figure 1. Flow diagram of included patients.
Note: Other includes spontaneous abortion, missed abortion, viable pregnancy, therapeutic abortion, molar pregnancy, or resolution of beta human chorionic gonadotropin serum level with no location documented.
ED = emergency department.

rupture, 7 (5.3%) required surgical management, 111 (84.1%) were successfully medically managed, and 2 (1.5%) patients had unknown outcomes .

DISCUSSION

Our results show that 17.8% of patients who received methotrexate failed initial treatment and required surgical management, and 11.2% had a subsequent ruptured ectopic pregnancy. Further investigation is needed to determine whether methotrexate failure was due to non-adherence to recommended guidelines or other unmeasured factors not accounted for in this study.

In this study, 13.2% of patients received methotrexate despite having one or more relative contraindications to methotrexate treatment, which may correlate with the higher failure rate.[5-7] Thus, patient education of the risk of methotrexate treatment failure is critical when management options are being discussed, particularly when methotrexate is being considered, despite known relative contraindications to medical management.

Despite having urgent and regular access to this institution's EPC, patients treated with methotrexate had high rates of return ED visits. Patients who failed methotrexate treatment had, on average, 1.7 return visits to the ED. This high proportion of unplanned return visits emphasizes the importance of ED providers being aware of ectopic rupture in patients undergoing treatment with methotrexate.

This study was conducted in a single-centre tertiary care institution with a high-acuity obstetrics program, and the results might not be generalizable to other settings. We did not include search terms, such as "first trimester bleeding," "vaginal bleeding," "pregnancy,"

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and "miscarriage," because we were interested in identifying only higher risk ED patients and describing their management. Therefore, these results should not be extrapolated to all ED patients experiencing first trimester complications. Due to the retrospective nature of this study, we can report only what was documented in the patient chart, and it is possible that clinical management may have been dictated by information not documented in the chart. Importantly, we are unable to comment on patient preferences that may have challenged standard of care and guided a patient's treatment plan.

CONCLUSIONS

Failure of methotrexate management often results in tubal rupture, need for urgent surgery, intra-abdominal hemorrhage, need for transfusion, and may be associated with future infertility and death.[2] Patient education of the risk of methotrexate failure is critical when management options are being discussed, particularly when methotrexate is being considered, despite known relative contraindications to medical management. Because these patients are likely to return to the ED for new symptoms, ED clinicians must also be aware of the risk of methotrexate failure and have a high index of suspicion for tubal rupture.

Author contributions: The authors all stand behind the conclusions of this manuscript, agree to be accountable for all aspects of the work, and support its publication. All authors contributed to the study conception and designed the protocol. All authors contributed to the manuscript preparation and have given approval for its submission.

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