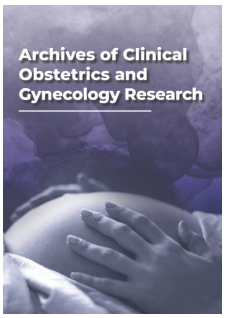
Archives of Clinical Obstetrics and Gynecology Research

Original Article



Utilizing Infusion Center For Medical Management of Ectopic Pregnancy

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Abstract

Introduction: *An ectopic pregnancy may be treated by methotrexate injection and/or surgery. Recent research indicates that two doses of methotrexate is more effective at resolving an ectopic pregnancy than a single dose.*

Methods: *We developed a protocol to allow patients to receive a second dose of methotrexate in the infusion center as opposed to the emergency department. We then conducted a physician satisfaction survey and retrospective data analysis.*

Results: *Time to resolution was not statistically significant between the one and two-dose groups. However, a significant amount of time was saved by patients when a second dose of methotrexate was given in the infusion center. Subsequently, physicians were more likely to prescribe two doses after implementing the procedural change.*

Discussion: *Two-dose protocol for methotrexate may be considered in outpatient centers as it is more time saving when compared to the ED for methotrexate injection.*

- Received Date: 04 Sep 2025
- Accepted Date: 10 Sep 2025
- Publication Date: 12 Sep 2025

Keywords: Ectopic pregnancy; Infusion Center; Methotrexate

Introduction

An ectopic pregnancy is a pregnancy that is found outside the uterus. The most common location of an ectopic pregnancy is the fallopian tubes [1] The estimated prevalence of ectopic pregnancy is 2% of all pregnancies, and it is estimated that ectopic pregnancies account for approximately 9% of maternal deaths during pregnancy in the United States [2]. Ectopic pregnancies are likely to be detected earlier as ultrasound modalities become more advanced and the risk factors for ectopic pregnancy are better understood. Traditionally, the mainstay treatment was surgical intervention, however, earlier detection allows for expanded use of medical therapy with methotrexate. Methotrexate is a folate antagonist that prevents the division of cells in the developing ectopic pregnancy [3].

There are several different proposed methotrexate treatment protocols including single dose, two-dose, or multi-dose [1]. While there are no strict guidelines on which protocol patients should be offered, patients with more risk factors for failure of medical management are usually offered the multi-dose regimen [4]. The single dose protocol has traditionally been preferred by physicians over the multi-dose protocol due to the need for less additional treatments and lower side effect profile despite the fact that the multi-dose regimen was proven to be more effective [4] Multi-dose protocol require methotrexate alternating with folinic acid to decrease the possible side effects. As an alternative, the two-dose protocol was developed in 2007 to keep the number of treatments low with lower risk of side effects than the multi-dosebut still provide the added benefit of increased likelihood of resolution of ectopic pregnancy [5].

Recent research indicates that a two-dose protocol of methotrexate treatment is more efficacious both in terms of successful resolution of ectopic pregnancy and time to resolution than a single dose protocol [6]

One recent meta-analysis looked at randomized controlled trials (RCT) that compared patients with an ectopic pregnancy who received both one and two doses of methotrexate [6]. The results showed that the two-dose protocol was associated with higher odds of treatment success than the single dose protocol and was more efficacious in the cases of higher serum beta-human chorionic gonadotropin (B-hCG) levels or large adnexal masses. The time to resolution of the ectopic pregnancy was also noted to be 7.9 days shorter in the two-dose protocol than the single dose protocol [6]. A randomized controlled trial of 200 patients diagnosed with ectopic pregnancies performed in Egypt found

Citation: Dowling J, Karki S, Kim C-S. Utilizing Infusion Center For Medical Management of Ectopic Pregnancy . Arch Clin Obs Gyn Res. 2025;4(2):008

a 90% overall treatment success with the two-dose regimen and a 78.75% success rate with the single dose regimen [7]. Additionally, time to resolution of the ectopic pregnancy was 10.8 days shorter with the two-dose regimen [7]. Another RCT of 100 patients with tubal ectopic pregnancies in Pakistan revealed no statistically significant difference between the one and two-dose methotrexate treatment protocols in terms of successful resolution of ectopic pregnancy, however, the time to resolution was 5.2 days shorter in the two-dose treatment group [8].

The increased efficacy of the two-dose treatment group is not without tradeoffs. The rate of surgery for unresolved ectopic pregnancies was not statistically significant between both the single and two dose protocol groups in the meta-analysis [6]. In addition, the two-dose protocol group was associated with higher odds of side effects [6], although the RCTs in both Egypt and Pakistan did not show a statistically significant difference in side effects between the two treatment protocols [7-8] The most commonly reported side effects associated with methotrexate are nausea, vomiting, diarrhea, and muscle weakness/cramps [3]

There is also the added patient burden of returning to the hospital for the second injection three days after the first injection. A recent case series found that methotrexate can be safely administered in an outpatient setting and had outcomes comparable to when it was administered in a hospital setting [9]. However, since many outpatient healthcare settings do not have methotrexate readily available, patients with a known ectopic pregnancy usually need to present to the emergency department (ED) to receive the second dose of methotrexate in a two-dose protocol.

Patient concerns in early pregnancy are known to make up a large proportion of overall Emergency Department visits [10]. One study found that pregnant patients account for 3% of all ED visits, estimated to be 2.77 million visits annually [10]. Another study found that ectopic pregnancies account for 1 in 7 ED visits during early pregnancy [11] or 12.3 per 1000 live births [12]. At a busy urban hospital such as our hospital, wait times in the emergency department can often be several hours long, especially for patients who are hemodynamically stable.

To examine the utility of an outpatient healthcare setting for providing medical treatment for ectopic pregnancy, a solution was proposed where patients were scheduled in the outpatient infusion center to receive the second dose of methotrexate of the two-dose protocol. The aim of this study is to explore our hospital's Obstetrics and Gynecologist (OB/GYN) physicians' satisfaction with both the single and two-dose methotrexate treatment protocols for ectopic pregnancy. Secondary aims of this study included time to resolution of ectopic pregnancy and time saved by patients.

Methods

Eligibility criteria

This study utilized an anonymous and voluntary cross-sectional survey sent electronically via email using Survey Monkey as well as a retrospective analysis of patients who received methotrexate as treatment for an ectopic pregnancy on patient outcomes. The inclusion criteria for the survey were OB/GYN resident physicians and OB/GYN hospitalist physicians who practice at Stamford Hospital. For retrospective analysis, patients documented with ectopic pregnancy (ICD-10 code O00.9) and treated with a single or two dose methotrexate treatment protocols were included in the study from July 2022-July 2024. Patients who had an ectopic pregnancy but did not receive methotrexate were excluded.

Data extraction

After receiving Institutional Review Board approval, the survey was sent to capture baseline healthcare professionals' preferences and understanding before the institutional change in July 2023 to two-dose protocol treatment of ectopic pregnancies in Stamford Hospital's infusion center. After administration of the baseline survey, educational materials, including the meta-analysis by Alur Gupta [6], was sent out to resident and hospitalist physicians to highlight the recent research showing the increased efficacy of the two-dose methotrexate protocol. Another follow-up survey was sent to gather healthcare professionals' preferences and understanding one year after the two-dose methotrexate protocol implementation utilizing hospital infusion center.

Retrospective data for this study was collected using electronic medical records and included patients' demographics information such as age, gestational age by last menstrual period (LMP). Clinical data included transvaginal ultrasounds for any evidence of an ectopic pregnancy (adnexal masses (yes/no)), as well as patient's laboratory values, specifically B-hCG levels >3,500 milli-international units per milliliter (mIU/mL) (yes/no) at time of first methotrexate injection. With regards to time spent in the ED and Infusion Center, time of the first set of vitals was recorded on each patient as well as time of methotrexate injection to calculate patient time spent in each location.

Variables and Instrument

The survey was designed to gauge baseline understanding and knowledge of different dosing regimens for medical therapy of ectopic pregnancy using methotrexate and perspectives on using single versus two-dose protocol at our institution. Both binary (yes/no) questions and Likert scale of 1 to 5 with responses of 1 being very difficult/not satisfied to 5 being very easy/completely satisfied were utilized. Surveys were emailed to 15 OB/GYN residents as well as 8 OB/GYN Hospitalist physicians via survey monkey. Informed consent for the study was received from each participant.

Patient outcomes variables were also investigated including time to resolution of ectopic pregnancy (days) which was calculated by counting the days from date of first dose of methotrexate to date of resolution (determined by B-hCG <5 mIU/mL). Wait time in ED and infusion center was also calculated by taking the difference of time between methotrexate injection and time of first set of vitals recorded.

Statistical Analysis

All statistical analyses were performed in SAS version 9.4. Descriptive statistics included the demographics of patients and survey responses. Data was presented in tables, including frequencies, mean and standard deviation. Chi-square tests were performed to assess differences in baseline and follow-up survey responses as well as differences in patient outcomes for methotrexate treatment (single dose vs two doses). Fisher's test was used when expected frequencies within cells were less than five patients/responses. Wilcoxon rank sum test was used to compare the differences in survey items with ordinal categories. Independent t-test was used to measure the difference in wait time and time to resolution (days) for two treatments. Non- parametric test was used in case of small

sample size within the group. Missing data were omitted, and there were no predetermined effect sizes for a formal power calculation to determine the number of subjects required for statistical significance. All analysis with resulting p-values <0.05 were considered statistically significant.

Results

Retrospective analysis of patients

A total of 27 patients met inclusion criteria, of which 13 (48%) were prescribed a single dose methotrexate treatment protocol and 14 (52%) were prescribed a two-dose methotrexate treatment protocol (Table 1). There was a significant difference in age between methotrexate treatment groups. The patients in the two-dose protocol group had a mean age of 31 years as compared to 27 years for single dose protocol group (p=0.03). No significant difference was found in gestational age by LMP (p=0.69).

Table 1. *Baseline demographics of patients with ectopic pregnancy*

Variable	Categories	Methotrexate treatment		p-value
		One dose n=13, 48% (Mean, SD)	Two doses n=14, 52% (Mean, SD)	
Age	Years	27.38 (4.75)	31.35 (4.43)	0.03*
Gestational age by LMP	Weeks	6.86 (0.89)	6.45 (1.75)	0.69*

LMP, last menstrual period.
Data shown in mean response with standard deviations (SD)
*Wilcoxon rank sum test

Table 2 presents the comparison of clinical characteristics of patients among the two treatment groups. Patients who were prescribed a single dose treatment regimen had higher number of suspicious findings for ectopic pregnancy seen on ultrasound, specifically adnexal masses with and without peripheral vascular flow, than patients who were prescribed a two-dose treatment regimen (46% vs 21%), however it was not statistically significant (p=0.24).

21% of patients who received two doses of methotrexate treatment had a B-hCG > 3,500 mIU/mL while zero patients from single dose treatment regimen were noted to have B-hCG >3,500 mIU/mL (p=0.22). Time to resolution was found to be significantly shorter in the single dose methotrexate treatment protocol than two-dose methotrexate treatment protocol (18 days vs 30 days) (p=0.005). However, when the patients in the two-dose group with B-hCG >3,500 mIU/mL were excluded from the analysis, the time to resolution was no longer statistically significant (18 days single dose vs 28 days two-dose) (p=0.06).

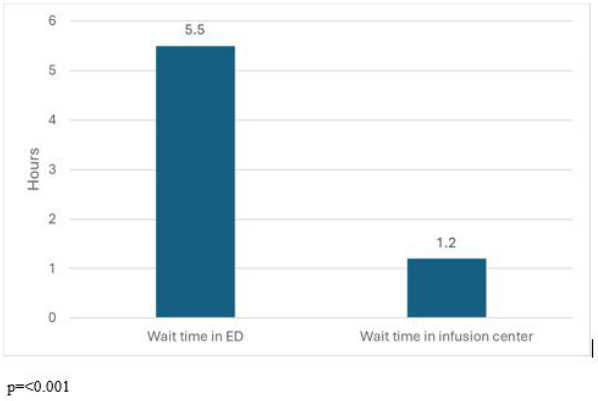

Figure 1: *Wait time in ED and infusion center for two doses of methotrexate*

When comparing the average wait time in the ED and infusion center for patients who received two doses of methotrexate treatment, the average wait time in the ED was significantly higher (333 mins =5.5 hours) than the average wait time in the infusion center (74 mins = 1.2 hours), or 259 minutes less (p=<.0001) (Figure 1).

OB/GYN residents and hospitalist physicians survey

The baseline survey was completed by 20 physicians, out of which 14 had valid responses with a response rate of 70%. The follow-up survey was completed by 18 physicians with 12 valid responses and a response rate of 66.67%. At the baseline survey, 92.86% mentioned using single dose protocol for medical management of ectopic pregnancy as their usual standard of care. This decreased to 41.67% in the follow-up survey, where more than half of the physicians (58.33%) mentioned using a two-dose protocol treatment as their standard of care (p=0.009) (Table 3). At the follow-up survey, 91.67%physicians felt that the process of receiving methotrexate was improved when the second dose could be given at the infusion center (Table 3). Other data obtained in the survey asked physicians to identify the factors preventing them from prescribing a

Table 2. *Clinical Characteristics of patients with ectopic pregnancy*

Variable	Categories	Methotrexate treatment		p-value
		One dose n=13	Two doses n=14	
Findings suspicious for ectopic pregnancy seen on ultrasound.	Yes No	6 (46.15%) 7 (53.85%)	3 (21.43%) 11 (78.57%)	0.24*
B-hCG >3,500 at time of 1st dose of MTX?	Yes No	0 13 (100%)	3 (21.43%) 11 (78.57%)	0.22*
Time to resolution	Days	18.22 (5.58)	30.25 (12.36)	0.005**

B-hCG, beta-human chorionic gonadotropin; MTX, methotrexate.
Data shown in count (%) or mean (standard deviation)
*Fisher's test **Wilcoxon rank sum

Table 3: *Survey items on dosing regimen*

Survey Items	Category	Baseline N=14	Follow-up N=12	p-value Fisher's test
In your practice, what dosing regimen do you use for medical management of ectopic pregnancy?	One	13 (92.86%)	5 (41.67%)	0.009
	Two	1 (7.14%)	7 (58.33%)	
Which methotrexate treatment protocol has the highest success for medical management of ectopic pregnancy?	Multidose regimen	1 (7.14%)	2 (16.67%)	0.78
	One	1 (7.14%)	0	
	Two	12 (85.71%)	10 (83.33%)	
Which methotrexate treatment protocol has the shortest time to resolution of ectopic pregnancy?	Multidose regimen	1 (7.14%)	0	0.99
	One	0	0	
	Two	13 (92.86%)	12 (100%)	
Did you switch from a one to two dose MTX regimen for treatment of ectopic pregnancy in the past year?	Yes	-	7 (58.33%)	n/a
	Case by case		5 (41.67%)	
Do you feel like the process of receiving methotrexate was improved now that the second dose can be given in the infusion center?	Yes	-	11 (91.67%)	n/a
	I did not transition to a two-dose protocol		1 (8.33%)	

MTX, methotrexate.
Data shown in count (%)

Table 4: *Ordinal survey items*

Survey Items	Category	Baseline SD	Follow-up (Mean, SD)	p-value (Wilcoxon Rank sum test)
How easy do you think the process is for patients to get MTX at TSH?	1 Very difficult – 5 Very easy	2.43 (0.85)	3.50 (1.17)	0.03
How expeditious do you think the process is for patients to get MTX at TSH?	1 Very time consuming – 5 Very expeditious	1.86 (0.77)	3.33 (1.23)	0.003
How satisfied are you with The Stamford Hospital's current avenues for receiving MTX therapy?	1 Not at all satisfied – 5 Very satisfied	2.36 (0.63)	3.91 (0.99)	0.005

SD, standard deviation; MTX, methotrexate; TSH, the Stamford Hospital.
Data shown in mean response with standard deviations (SD)

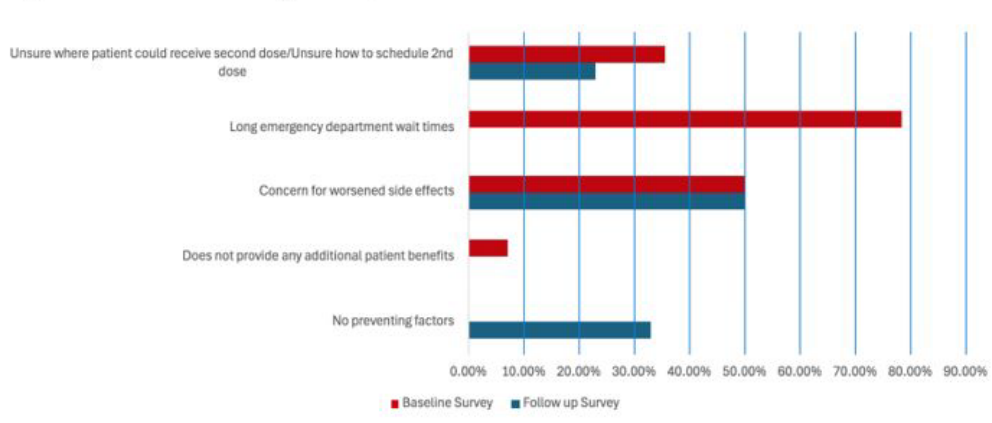

Figure 2: *Factors Preventing Prescription of Two-Dose Methotrexate Protocol*

two-dose regimen of methotrexate. In the baseline survey, 78% of physicians indicated long ED wait times as a barrier and 23% indicated they were unsure where a second dose could be administered. In the follow up survey, 33% of respondents stated there were no preventing factors to prescribing two doses while 35% stated they were unsure how to go about scheduling the second dose in the infusion center. Another factor that seemed to deter physicians from prescribing two doses of methotrexate was concern for worsened side effects. In both the baseline and follow-up surveys, 50% of respondents indicated that concern for side effects impacted their decision (Figure 2).

Table 4 shows physician satisfaction with regards to the process of receiving methotrexate at Stamford Hospital. The process for patients to get methotrexate at Stamford Hospital was significantly improved to 'somewhat easier' in follow-up period from 'somewhat difficult' in baseline period (p=0.03). Similarly, the process to get methotrexate at Stamford Hospital was significantly improved in follow-up period from 'somewhat time consuming' in baseline period to 'no opinion' in follow up period (p=0.003). Physicians were 'somewhat satisfied' with the hospital's current avenue for receiving methotrexate therapy at the end of the follow-up period as compared to 'somewhat unsatisfied' in baseline period, a significant difference (p=0.0005).

Discussion

In this study, we anticipated that the two-dose methotrexate regimen would be associated with shorter time to resolution of ectopic pregnancy. We found that the time to resolution of ectopic pregnancy was shorter in the single dose regimen group as opposed to the two-dose regimen group. While these results are incongruent with similar studies, there are several reasons and limitations of our study to explain this. When the initial B-hCG level of patients is factored into account, our results are more analogous with what previous studies have shown. Higher B-hCG levels are often associated with higher rates of medical treatment failure with regards to ectopic pregnancies [13]. In this study, there were three patients in the two-dose group who had B-hCG >3,500 mIU/mL. When these patients were eliminated from the data analysis to match the groups, the time to resolution findings were no longer considered statistically significant. Another reason our results may differ from previous studies is the lack of randomization between our two groups. Given this was not a randomized controlled trial as most studies preceding ours but rather a retrospective data analysis, our groups were found to be different in several characteristics. There was a statistically significant difference in age between the two groups with the single dose group being younger than the two-dose group. This could be contributing to the unexpected results as older age has been shown to be associated with higher risk of medical treatment failure of ectopic pregnancy [14], although treatment failure was not seen in any of our patients in either treatment group.

While there was no statistically significant difference in time to resolution of ectopic pregnancy between the two groups, our results are not insubstantial. They demonstrate that those with higher starting B-hCG levels benefit from the two-dose protocol with similar outcomes to those with lower starting B-hCG levels. Furthermore, the difference in time spent in the ED versus the infusion center at Stamford Hospital was astonishing. Time spent waiting by patients could not be compared between the two treatment groups as the patients who received a single dose of methotrexate only had it in administered in the ED. However, for the patients who received two doses of methotrexate, with the first dose being given in the ED and the second dose in the infusion center, patient wait time in each location could be calculated and compared. Overall, the data shows that on average, patients were required to wait nearly 4.5 hours less in the infusion center as opposed to the emergency department.

The second part of this study was a physician satisfaction survey to ascertain whether OB/GYN physicians employed by Stamford Hospital thought that the new avenue for methotrexate administration was a positive change. The findings indicate that the physicians think that giving methotrexate injections in the infusion center is more convenient for patients.

More physicians at our hospital began transitioning to a two-dose protocol of methotrexate for medical treatment of ectopic pregnancy after distribution of educational materials. Prior to the policy change, only 7% of physicians routinely used a two-dose protocol, however, after the policy change with the ability to now give methotrexate injections in the infusion center, 58% of physicians indicated they started routinely prescribing a two-dose protocol. The infusion center at our hospital is open seven days a week from 9am to 5pm, providing flexibility in scheduling patients, which we believe encouraged buy-in from physicians to transition to a two-dose protocol.

There are several limitations to this study. Primarily, the sample size is very small both with regards to number of patients who got either one or two doses of methotrexate between the years 2022-2024, but also with regards to the number of physicians who completed the survey. In addition to the small sample size, several patients were also lost to follow up during the course of this study and time to resolution of their ectopic pregnancy could not be determined. The age and initial B-hCG levels of the patients were dissimilar between groups as well, confounding the time to resolution results. This study is also a single institution study. Based on additional demographic information collected on the patients, nearly all of them were either uninsured or on Connecticut state low-income medical insurance. While these patients do make up a large proportion of Stamford's population, this group is not demonstrative of the general population in the area. Furthermore, our two-dose protocol group did not include patients who received both doses at the infusion center for comparison, as all ectopic pregnancies were initially diagnosed in the ED. Similarly, of the physicians who were surveyed, many of the respondents are residents being trained at Stamford Hospital and therefore have been taught very similar management styles that might not be the same as management styles at a different institution.

Future directions for this study include comparing the cost difference when patients receive methotrexate in the ED compared to when they get it in the infusion center. Billing codes could not be obtained for this study and therefore the price difference for patients could not be estimated. It would also be interesting to compare the hospital cost of giving the injection in the ED compared to the infusion center. Another future direction of this study could be investigating patient satisfaction with regards to receiving injections in the ED versus the infusion center. Since the protocol change allowing methotrexate injections to be given in the infusion center, Stamford Hospital OB/GYN department has started using the infusion center to give treatments to patients who have been diagnosed with medical conditions and require treatment, but do not need to see a doctor every time they receive a

treatment. Examples include betamethasone injections for fetal lung maturity, intravenous iron for patients with anemia, and Rhogam to prevent alloimmunization. Future studies could look at the price differential for these treatments when given in the infusion center as opposed to an acute care setting as well as analyze patient and physician satisfaction.

Conflicts of interest

There are no conflicts of interest amongst any of the authoring physicians.

Acknowledgements

No additional authors contributed to the writing of this manuscript. We have no financial disclosures.

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