Methotrexate Administration to Patients With Presumed Ectopic Pregnancy Leads to Methotrexate Exposure of Intrauterine Pregnancies

Dmitry Fridman, MD, PhD, Eleanor Hawkins, MD, Peer Dar, MD, Scott Chudnoff, MD, Ohad Rotenberg, MD, Woojin Chong, MD, Xianhong Xie, PhD, Sukrant Mehta, MD, Mark Levie, MD

Objective—To report clinical experience with methotrexate (MTX) treatment for suspected but not definite ectopic pregnancy (EP).

Methods—This was a retrospective cohort study. All patients treated with MTX for presumed EP between 2000 and 2016 were included. Demographic, clinical, sonographic, and outcome data were collected and analyzed.

Results—A total of 820 patients were treated with MTX, 692 (84.4%) of which were lacking definitive features of EP; 155 (22.4%) failed to follow up until complete resolution and were excluded. Retrospective sonographic categorization was applied to 537 patients; of those patients, 393 (73.2%) were categorized as probable EPs, 136 (25.3%) pregnancies of unknown location (PULs), and 8 (1.5%) probable intrauterine pregnancies (IUPs). Sixteen were eventually diagnosed with IUP: 6 from the probable EPs, 9 from the PULs, and 1 from the probable IUP group. Patients with final diagnosis of IUP had higher values of β–human chorionic gonadotropin as well as lower prevalence of adnexal mass (38% versus 74%; $P = .003$), higher prevalence of intracavitary fluid (44% versus 9%; $P = .0004$) and thicker endometrium (17.1 ± 11.8 versus 9.7 ± 5.6; $P = .04$). None of the sonographic parameters were able to distinguish patients with IUP. One patient of the 16 with IUP was diagnosed with a viable pregnancy, and 7 additional patients had a possible viable pregnancy. None of them elected to continue the pregnancy.

Conclusions—Most patients with suspected EP who are eligible for medical treatment lack definitive sonographic features of EP. Treatment with MTX in such cases should be delayed, as clinically reasonable, to improve the diagnosis and prevent inadvertent administration of MTX to patients with a viable IUP.

Key Words—ectopic pregnancy; methotrexate; pregnancy of unknown location

Despite advances in early diagnosis and treatment, ectopic pregnancy (EP) is the most common cause of maternal mortality during the first trimester in the United States.[1] The use of methotrexate (MTX), a folic acid antagonist, in the treatment of EP has significantly expanded since its first description.[2] In 2002, only 11% of EPs were treated with MTX; by 2007, over 35% of patients received this treatment.[3] Medical treatment of EP is better tolerated and is associated with lower cost, lower morbidity, and potentially better fertility preservation than surgical management.[4–6]

Received February 26, 2018, from the Department of Obstetrics, Gynecology, and Women's Health, Montefiore Medical Center, Bronx, New York, USA (D.F., E.H., P.D., S.C., O.R., W.C., X.X., S.M., M.L.); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, USA (X.X.). Manuscript accepted for publication July 14, 2018.

Address correspondence to Dmitry Fridman, Duke University Medical Center, Department of Obstetrics and Gynecology, 200 Trent Dr, Durham, NC 27710 USA.

E-mail: dmitry.fridman@gmail.com

Abbreviations

β-hCG, β–human chorionic gonadotropin; EP, ectopic pregnancy; IUP, intrauterine pregnancy; MTX, methotrexate; PULs, pregnancies of unknown location (PUL)

doi:10.1002/jum.14751

When pregnancy location is unknown at the time of the first visit, waiting expectantly for a definitive diagnosis by either visualization of extrauterine or intrauterine gestation[7] or by observing a rise of β–human chorionic gonadotropin (β-hCG) following uterine cavity evacuation is recommended.[8] In a consensus statement on pregnancy of unknown location (PUL),[9] the International Society for Ultrasound in Obstetrics and Gynecology emphasized that a single-visit approach to the management of PULs is not appropriate.

While expectant management has been the recommended practice for PULs since 1999,[7] a desire to address noncompliance and to avoid uterine evacuation, associated with its own risks and complications, poorer transvaginal ultrasonography capabilities, and sometimes unfounded concern for possible and imminent rupture of an EP may lead to administration of MTX before a definitive diagnosis is made. Those cases are sometimes described as presumed EP, and despite the criticism of this concept,[10,11] in clinical practice as well as in many studies, it is still widely utilized.[12,13] It is no wonder than that the combined increase in utilization of MTX and lack of adherence to use of definitive diagnostic criteria has led to accidental exposure of early IUPs to MTX. In cases of desired IUP, this can cause irreparable malformation or miscarriage.[14]

The literature on experience with medical management of presumed EP[8] and the inadvertent administration of MTX to patients who are later diagnosed with IUP is limited.[14–18] The objective of this study was to report on our experience with medical management of all cases with presumed EP and the incidence and causes of inadvertent administration of MTX to patients who are later diagnosed with IUP in a large, inner-city tertiary center.

Materials and Methods

This study is a retrospective cohort analysis of all cases in which MTX was given in our medical center to patients treated for presumed EP. Montefiore Medical Center serves a population in the Bronx and Westchester in New York State and includes 3 hospitals with the same providers cross covering among those facilities. All the protocols of management in regards to presumed EP are synchronous among those facilities. Presumed EP included cases of probable EP, PUL, or probable IUP, based on a 2011 consensus statement of nomenclature of PUL.[8] Briefly, probable EP is diagnosed when an inhomogeneous adnexal mass or extrauterine saclike structure is seen, PUL when no signs of either EP or IUP are seen, and probable IUP when an intrauterine echogenic saclike structure is visualized. Patients with definite EP were excluded. Definitive diagnosis of EP included either visualization of extrauterine yolk sac and/or fetal pole, or a rise of β-hCG following uterine cavity evacuation.

All patients were evaluated in the settings of an emergency room, and an OBGYN consulted on all the patients before MTX administration. All patients underwent both transabdominal and transvaginal sonography within hours (generally 2 to 3) after initial evaluation by a physician. Laboratory analysis (including quantitative β-hCG) were available during ultrasound examination. All the transvaginal sonographic studies were performed by a certified technician and read by a radiology resident supervised by a radiology attending physician. There were no discrepancies between the resident and attending physician read in our study. Scans were performed according to the American Institute of Ultrasound Medicine's Practice Parameter for the Performance of Ultrasound of the Female Pelvis. We analyzed a convenience sample of patients treated during the 16-year period between January 2000 and December 2016. Because it was a retrospective review and identifying information was not stored, no consent was sought. The study was approved by the Montefiore Medical Center Institutional Review Board.

Data collection was performed using Clinical Looking Glass, an interactive software query system developed at our institution.[19] The initial patient selection was conducted by identifying the hospital pharmacy records of patients who received MTX with a positive β-hCG within 10 days of MTX administration. Subsequently, manual review of retrieved charts was performed to acquire demographic and clinical information, reports of laboratory workup, sonography reports, and pathologic examination reports.

Based on manual review of sonographic findings on the date of MTX administration, patients with presumed EP were analyzed. We excluded those patients who did not follow up within our institution until resolution of their pregnancy.

Our protocol of management of patients following MTX administration (day 1) included follow-up on days 4 and 7 with clinical examination and evaluation of β-hCG levels. In case there was a 15% decrease of β-hCG from day 4 to day 7, weekly follow-up was commenced until resolution of pregnancy (β-hCG less than 15 IU or negative urine pregnancy test). During follow-up, sonography was performed only if clinically indicated (worsening pain, concerning findings on exam, or plateauing β-hCG levels). The sonographic categorization (probable EP, PUL, probable IUP) was applied retrospectively, following data collection using definitions based on a 2011 consensus statement of nomenclature of PUL.[8] At the moment of initial treatment with MTX, all patients were treated for presumed EP. Categorization was based upon descriptive sonographic findings (ultrasound report), rather than images. All cases with saclike intracavitary fluid were categorized as probable IUP regardless of presence of an adnexal mass. There was no discrepancy among coauthors regarding categorizing the cases.

Among patients subsequently diagnosed with an IUP, we defined a viable IUP as one with a fetal pole with visualized fetal heartbeat. Potentially viable IUP was defined in case MTX was administered upon the first day of observation or if an adequate rise of β-hCG was observed accompanied by development of intrauterine saclike structure.

Patients who received MTX and were later diagnosed with IUP comprised the study group and were compared to all other patients with an initial diagnosis of presumed EP, that is, the control group. Groups were compared for patient and gestation characteristics as well as for sonographic findings and final outcome. Comparison between groups was performed using the following tests: for categorical variables (demographic parameters), the chi-squared test or Fisher exact test (if $n \leq 5$) were applied as appropriate. For continuous variables (β-hCG levels, length of amenorrhea) we anticipated normal continuous distribution, and data were expressed as mean and standard deviation, independent samples t test. Adnexal masses were compared as present versus absent and also based on size as less than 20 versus 20 to 40 versus greater than 40 mm if present. Level of β-hCG was reported as a categorical variable with levels: less than 500, 500 to 1000, 1000 to 1500, 1500 to 2000, 2000 to 5000, or greater than 5000 IU. A P value of less than .05 was used a threshold for defining differences as statistically significant. Statistical software (SAS 9.3; SAS Institute, Cary, NC) was used for statistical analysis. The individual clinical course was reported for outstanding cases.

Results

A total of 820 patients received MTX in association with a positive pregnancy test during the study period. Of these, 692 (84.4%) had presumed EP, and 155 (22.4%) did not follow up in our institution to complete resolution of pregnancy and were excluded, which left us with 537 available cases for complete analysis. Retrospectively, a sonographic categorization

Table 1. Patient Categorization by Initial Diagnosis and Final Outcome

Initial Diagnosis	Patients, n (%)	Distribution of Final Outcome by Initial Diagnosis	Final Outcome	Patients, n (%)
Definite EP	0		Confirmed EP	156 (29.0%)
Probable EP	393 (73.2%)	Confirmed EP –106 Medically treated PUL –281 Histologic IUP –6		
PUL	136 (25.3%)	Confirmed EP –48 Medically treated PUL –79 Histologic IUP –9	Medically treated PUL	365 (68.0%)
Probable IUP	8 (1.5%)	Confirmed EP –2 Medically treated PUL –5 Histologic IUP –1		
Definite IUP	0		Confirmed IUP	16 (3.0%)

EP indicates ectopic pregnancy; IUP, intrauterine pregnancy; and PUL, pregnancy of unknown location.

was done and 393 patients were categorized as probable EP, 136 as PUL, and 8 as probable IUP (Table 1). A total of 156 were confirmed as EP following a subsequent sonogram, negative curettage for products of conception, or through visualization on laparoscopy. Sixteen were histologically confirmed as IUP: 6 from the probable EP group, 9 from the PUL group, and 1 from the probable IUP group. At least 8 (1.5%) patients of the entire cohort had a viable or potentially viable IUP, and 365 patients remained without definitive diagnosis.

Of the 537 patients, 155 received MTX on the day of diagnosis, 142 received MTX despite decreasing β-hCG, and 131 received MTX for rising β-hCG levels that were still below 1500 IU/L.

Patients with a histologic IUP were similar to controls with respect to demographic data, clinical presentation, and past medical history (Table 2). We did not detect a statistically significant difference in the proportion of patients with histologic IUP between earlier (years 2000–2010) and later (years 2011–2016) cohorts (3.6% and 2.4%, respectively; $P = .41$). In analyzing laboratory data, a significantly higher proportion of patients in the study group had β-hCG levels above 1500 on the date of MTX administration (75% versus 39%; $P < .01$).

There was no significant difference in timing of MTX administration—4 (25%) of 16 cases with subsequently diagnosed histologic IUP received MTX at the first encounter, similar to controls (29%; $P = .74$).

On sonography (Table 3), study patients had a significantly lower prevalence of an adnexal mass and a higher frequency of any intracavitary fluid, including spindle-shaped fluid, suggestive of hematometra rather than a gestational sac. Patients with a subsequently diagnosed histologic IUP had a thicker endometrium, though no clear cutoff value was identified. The clinical course of patients subsequently diagnosed with histologic IUP is detailed in Table 4.

Of the 16 patients who received MTX and were subsequently diagnosed with an IUP, 8 (50%) had a viable (patient 1) or potentially viable (patients 2–8) IUP. Four patients (patients 1–4) received MTX on the first day, and another 4 (patients 5–8) had an increase of their β-hCG levels, accompanied by visualization of intrauterine saclike structure following

Table 2. Demographic and Clinical Characteristics

Variable	Combined group (n = 521)	Histologic IUP (n = 16)	*P* value
Age, mean (SD)	29.7 (6.3)	30.5 (6.7)	.63
History of STD (%)	125 (24%)	6 (37.5%)	.22
History of EP (%)	83 (16%)	1 (6.3%)	.48
History of pelvic surgery (%)	172 (33%)	5 (31.3%)	0.98
BMI, mean (SD)	29.5 (6.6)	29.9 (4.3)	.81
Length of amenorrhea, mean (SD)	44.6 (11.8)	41.8 (9.6)	.40
Complaint of pain (%)	417 (80%)	12 (75%)	.52
Bleeding pattern (%)			.30
Mild or none	479 (92%)	14 (87%)	
Moderate or heavy	42 (8%)	2 (13%)	
β-hCG (%)			.01
0 to 500 IU	198 (38%)	2 (13%)	
500 to 1000 IU	68(13%)	2 (13%)	
1000 to 1500 IU	52 (10%)	0	
1500 to 2000 IU	31 (6%)	4 (25%)	
2000 to 5000 IU	99(19%)	4 (25%)	
>5000 IU	73 (14%)	4 (25%)	
First encounter administration (%)	151 (29%)	4 (25%)	.74

β-hCG indicates β–human chorionic gonadotropin; BMI, body mass index; EP, ectopic pregnancy; IUP, intrauterine pregnancy; SD, standard deviation; and STD, sexually transmitted disease.

Table 3. Sonographic Findings Before Methotrexate Administration

	Combined Group (n = 521)	Histologic IUP (n = 16)	*P* value
Sonographic categorization (%)			.003
Probable EP	387 (74.3%)	6 (37.5%)	
PUL	127 (24.4%)	9 (56.2%)	
Probable IUP	7 (1.3%)	1 (6.3%)	
Intrauterine saclike fluid (%)	9 (2%)	1 (6.3%)	.25
Intrauterine spindle-shaped fluid (%)	36 (7%)	6 (37.5%)	.001
Any intrauterine fluid (spindle and saclike) (%)	45 (9%)	7 (43.8%)	.0004
Presence of adnexal mass	387 (74.3%)	6 (37.5%)	.003
Size of adnexal mass if present (%)			.67
<20 mm	159 (30.5%)	2 (13%)	
20-40 mm	195 (37.4%)	3 (18.8%)	
>40 mm	35 (6.7%)	1 (6.3%)	
Amount of free peritoneal fluid			.92
None or small	485 (93.1%)	15 (93.7%)	
Moderate or large	36 (6.9%)	1 (6.3%)	
Endometrial thickness mean (SD), mm	9.7 (5.7)	17.1 (11.8)	0.04

EP indicates ectopic pregnancy; IUP, intrauterine pregnancy; PUL, pregnancy of unknown location; and SD, standard deviation.

MTX administration. It is unclear if that saclike structure was a de novo development or was missed on initial sonogram. All those receving MTX on the first day had β-hCG values above 3000 IU, and patients 2 through 4 had levels above 5000 IU. Patients 5 and 6 had MTX administered on their second encounter (day 3 of observation), when both reported worsening of abdominal pain and sonography did not demonstrate an IUP but a new adnexal mass, which precipitated administration of MTX. In patients 7 and 8, a β-hCG trend was interpreted as inadequate based on the contemprorary literature. After an IUP was detected, all patients were counseled on MTX effect on pregnancy and the high risk of fetal malformations should the pregnancy continue. Following the counseling, none of the patients elected to continue the pregnancy.

Seven patients (patients 9–15) had an unlikely viable pregnancy at the moment of MTX administration (plateauing or decreasing levels of β-hCG). Of these, most (5 of 7 [patients 11–15]) received MTX immediately following a uterine evacuation with scant material, and only subsequently pathologic examination revealed products of conception. Patient 9 had an endometrial biopsy that was negative for products of conception, so MTX was administered; subsequently, because of continued plateauing β-hCG, the patient underwent uterine evacuation. Patient 10 had free pelvic fluid and a corpus luteum cyst mimicking EP (Figure 1) on follow-up sonogram and was taken to the operating room, where she underwent a negative diagnostic laparoscopy and dilation and curettage (returned products of conception). Patient 16 elected to have a uterine evacuation rather than expectant management and received MTX following scant material of dilation and curettage.

It should be noted that among patients subsequently diagnosed with histologic IUP, in 6 cases (nos. 1, 5, 6, and 10–12) an inhomogenous adnexal mass highly suspicious for EP was reported on the sonogram (Figures 1 and 2).

Discussion

In the large cohort reported here, of patients treated with MTX in concurrence with positive pregnancy, the majority of patients had no definitive features of EP. Only 29% of patients with presumed EP and treated with MTX were eventually confirmed as EP, and 8 (1.5%) patients had a viable or potentially viable IUP.

Overall, we identified 16 patients with IUP through histology but aware that the actual number of IUP in population of patients with presumed EP is significantly higher. Studies evaluating universal uterine evacuation in patients with presumed EP showed that that more than a third actually had an IUP.[10,11]

Although uncommon, treating presumed EP with MTX just to find out this was a viable IUP is tragic. In our study, we could not identify demographic or clinical variables that would reliably assist in distinguishing women with an IUP among those who have no definitive diagnosis of either EP or IUP on initial presentation. This finding is concordant with the data of Shaunik and colleagues[11] as well as Condous and colleagues.[20] Patients with the eventual diagnosis of a histologic IUP had substantially higher values of β-hCG than all others, but we did not detect a cutoff zone that would be distinguishing. It is clear that using a discriminatory zone alone or a plateauing β-hCG is unreliable to distinguish the location of the pregnancy and leaves significant room for misdiagnosis. The recent transition in terminology from presumed EP to 3 subcategories (Probable EP, PUL, and Probable IUP)[8] was an important step in the right direction but did not resolve the problem. In our cohort, we identified IUP in each of the subcategories, and only 1 of 8 patients with probable IUP was confirmed as such.

One of the most worrisome findings in our study was that visualizing an inhomogeneous paraovarian mass did not necessarily exclude IUP. In fact, 37.5% (6 of 16) of the patients diagnosed with histologic IUP were initially categorized as probable EP based on sonography. Differential diagnosis of an adnexal mass always includes hemorrhagic or corpus luteal cysts, which might make the diagnosis challenging in the case of exophytic localization (Figures 1 and 2).[21] This observation supports the conclusions of other authors[11,21] that even though nondefinitive sonographic findings can be predictive of a final outcome, they are not exclusive and cannot be reliably used to differentiate location of the pregnancy.

The most consistent sonographic finding in association with IUP was the presence of any type of

Table 4. Detailed Description of Patients With Histologic IUP Who Received Methotrexate

Case Number	Age	Parity	GA	Day 1 β-hCG	MTX day	MTX β-hCG	MTX sono categorization	Size of mass (mm)	D&C day	Narration
1	33	0	6W2D	3107	1	3107	Probable EP	22	23	Following MTX, noted inappropriate rise of β-hCG and interval development of IUP with FH; elected for termination of pregnancy
2	34	1	5W2D	6859	1	6859	PUL	N/A	5	Following MTX noted inappropriate rise of β-hCG and an interval development of growing intrauterine sac; underwent D&C with POC
3	27	2	5W2D	5788	1	5788	Probable IUP	N/A	6	Initially, the intrauterine sac was considered a false sac. Following MTX noted inappropriate rise of β-hCG and growth of intrauterine sac; underwent D&C with POC
4	17	0	9W3D	7110	1	7110	PUL	N/A	1	Underwent D&C with scant pathologic examination, received MTX same day, subsequently pathologic examination returned POC
5	26	3	6W2D	1082	3	1775 (64% increase)	Probable EP	31	14	Had a new adnexal mass detected day 3. Following MTX presented with heavy vaginal bleeding; underwent D&C with POC
6	34	2	5W3D	252	3	600 (138% increase)	Probable EP	28	9	Patient declined D&C, persistent heterogenous adnexal mass, following MTX noted a growing intrauterine sac and rise of β-hCG; underwent D&C with POC
7	29	4	6W3D	492	5	888 (41% increase)	PUL	N/A	7	Following MTX noted inappropriate rise of β-hCG and an interval development of growing intrauterine sac; underwent D&C with POC
8	34	1	4W2D	1302	5	1590 (21% increase)	PUL	N/A	16	Following MTX noted inappropriate rise of β-hCG and an interval development of growing intrauterine sac; underwent D&C with POC
9	43	1	UK	1231	6	1863 (9% increase)	PUL	N/A	33	Had EMB on fourth visit, negative for POC followed by MTX, subsequently noted intrauterine fluid collection, plateauing of β-hCG; underwent D&C with POC
10	23	1	6W5D	4133	2	4046 (2% decrease)	Probable EP	19	7	Following MTX noted plateauing of β-hCG and development of free fluid, was taken for diagnostic laparoscopy, D&C; on laparoscopy, small amount of free fluid, no evidence of ectopic, D&C returned with POC
11	32	0	4W6D	3360	2	2056 (39% decrease)	Probable EP	77	2	On day 2 a new adnexal mass was seen on sono, patient underwent D&C with scant pathologic examination same day, received MTX, subsequently pathologic examination returned POC
12	26	2	5W5D	2109	4	2099 (25% decrease)	Probable EP	8	3	Underwent D&C with scant pathologic examination, received MTX same day, subsequently pathologic examination returned POC
13	29	4	6W3D	260	5	243 (12% increase)	PUL	N/A	5	Underwent D&C with scant pathologic examination, received MTX same day; subsequently, pathologic examination returned POC
14	42	1	UK	409	10	1692 (12% increase)	PUL	N/A	10	Underwent D&C with scant pathologic examination, received MTX same day; subsequently, pathologic examination returned POC
15	25	0	4W2D	475	3	488 (3% increase)	PUL	N/A	3	Underwent D&C with scant pathologic examination, received MTX same day; subsequently, pathologic examination returned POC
16	34	2	UK	4377	3	5453 (25% increase)	PUL	N/A	3	Elected for D&C rather than expectant management, following scant materials, received MTX on the same day; subsequently, pathologic examination returned POC

β-hCG indicates β–human chorionic gonadotropin; D&C, dilation and curettage; EMB, endometrial biopsy; EP, ectopic pregnancy; FH, fetal heartbeat; GA, gestational age; MTX, methotrexate; N/A, not applicable; POC, products of conception; PUL, pregnancy of unknown location; UK, unknown.

intrauterine fluid. Benson and colleagues[22] suggest that clearly intracavitary fluid with echoes and/or pointy edges represents blood or secretion, while anechoic cystic structures represent an early gestational sac. In our data, patients who were subsequently diagnosed with an IUP had a significantly higher proportion of any described shape of intrauterine fluid (44 versus 9%; $P = .0004$). Therefore, in the case of plateauing β-hCG levels (suggesting abnormal gestation), the presence of any endometrial fluid is suggestive of an IUP.

Four of our 16 patients with a subsequently diagnosed IUP, including the only viable IUP in this data set, received MTX on their first visit. We agree with the statements made by Condous and colleagues[20] and Barnhart,[23] who suggest that there is almost no reason to give MTX on the first encounter with the patient. Furthermore, waiting for a repeat β-hCG will identify the large group with a spontaneous decrease in β-hCG, who can be spared intervention and its potential sequelae.[24] Avoiding MTX on the day of initial diagnosis is probably the most critical step in the management of these patients.

A value of routine uterine evacuation prior to administering MTX to patients with presumed EP is debated. In this report, 172 (32%) underwent uterine evacuation. This practice is advocated by some authors, as it decreases the risk of inadvertent MTX administration, provides definitive diagnosis, and shortens follow-up when IUP is diagnosed. In the long run, routine evacuation also helps to avoid mislabeling some women with a history of EP, which may

Figure 1. Inhomogenous adnexal mass (patient 11) mistaken for ectopic pregnancy. A complex mass **(A)** composed of a hemorrhagic corpus luteum cyst (CL) and blood clots (BC) surrounding the ovary that can resemble an ectopic pregnancy. Adding color Doppler **(B)** might not be beneficial, as corpus luteum and ectopic pregnancy share a similar appearance.

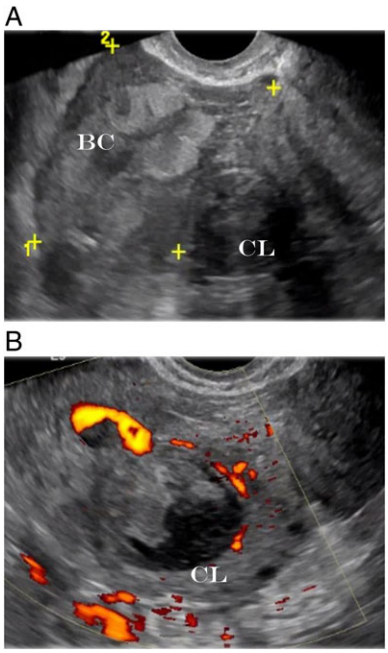
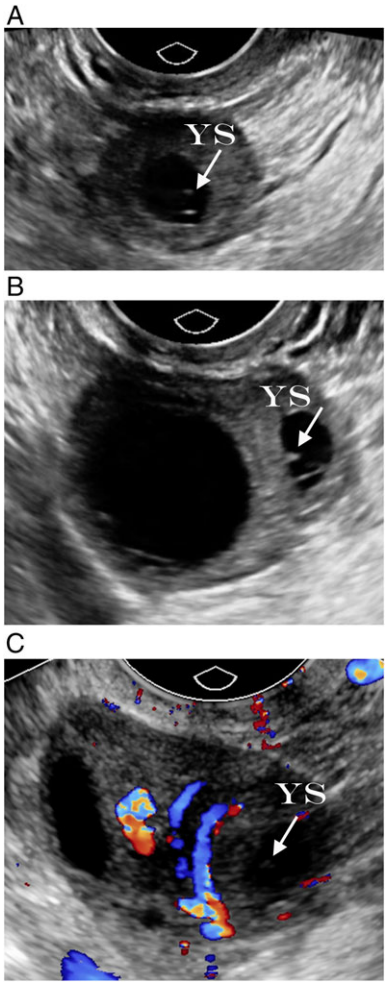


Figure 2. Corpus luteum cyst mimicking an ectopic pregnancy (patient 10). Using a single 2-dimensional view (**A**), a saclike structure with a "yolk sac" (YS) was seen and read as an "isolated" structure near the right ovary. Additional views (**B, C**) show that the mass was not isolated but an exophitic corpus luteum cyst within the right ovary.



alter their reproductive management.[10,11] The downsides of performing universal uterine evacuation are a higher rate of invasive surgical procedures with a low but possible associated risk, reliance on compliance, and a longer time of direct provider involvement. In our cohort, performing uterine evacuation did not completely exclude the possibility of inappropriate MTX exposure to a patient, as MTX was administered immediately after uterine evacuation. While the practice of uterine evacuation may have a role in the management of presumed EP, it is likely a limited one and its use will probably become uncommon, as is now the case in most European countries.[8] If a provider decides to perform uterine evacuation, we advise delaying administration of MTX for 24 to 48 hours and analyzing the level of β-hCG after that time. The use of endometrial biopsy rather than dilation and curettage is especially discouraged because it can miss a very early IUP, as was seen in 1 of our cases.

Although not investigated in this study, there are 2 topics that require further attention and investigation. The first is the overuse of MTX seen in this cohort. Cases like first-day treatment, decreasing levels of β-hCG, and rising levels below 1500 in nonsymptomatic patients comprised a significant proportion of our population (79.7%). The reasons for this finding require further investigation. It is possible that high noncompliance rate in urban populations (22.4% in our study, 14.1–54.5% in similar populations)[25,26] may play a role in this behavior. Other reasons, such as litigation anxiety, availability of the operating room, and availability of high-level consultative support, are among possible causes that require further investigation.

The second concern is the level of training and experience in transvaginal sonography of early pregnancy for gynecologists in the United States. In this cohort, we had at least 1 case in which a fetus with a heartbeat was seen just a few days after the administration of MTX. This clearly suggests that a gestational sac was already present at least in 1 case but was missed at the time of treatment. In 6 additional cases, a sac was seen for the first time after the administration of MTX, and in 2 of these cases the β-hCG levels were above 3000 IU/L at the time of treatment, which raises a concern that a gestational sac was also missed in those cases. While gynecologists in the United States are considered trained in vaginal sonography by the end of residency, there is no mandate to complete such training. It was only this year that a curriculum for ultrasound training in obstetrics and gynecology was developed and recommended by several of the relevant professional societies.[27] While this is an excellent step to improve the quality of ultrasound performance, we believe that this is still another reason for delayed treatment in cases eligible for medical management.

The main strengths of our study include its large sample size, strict diagnostic criteria applied, heterogeneity of providers involved in care of the patients, and diverse inner-city population.

The main limitation of this study is its retrospective nature, which leads to significant loss of insight into the decision-making process. To help address this shortcoming, all notes were reviewed in an attempt to gain understanding of the decision-making process.

A second limitation is the high number of patients who did not follow up in our institution. Indeed, compliance with follow-up in inner-city hospitals among patients treated for EP is quite low.[25,26] The noncompliance could misrepresent a proportion of histologic IUP by both artificially decreasing the prevalence (patients who discovered management error decided to follow up elsewhere) and by artificially increasing the prevalence (asymptomatic patients decided to quit follow-up care).

Our study comes from a single urban hospital system, so generalizability potentially could be limited. Conversely, our center serves a diverse inner-city population and staffs a multitude of physicians with different training backgrounds. That allows us to suggest that our results can be generalized to other urban medical centers.

Finally, sonographic findings were interpreted over several years in different hospitals by different providers and without a uniform reporting system. Only reports were available for interpretation. To overcome this limitation, we retrospectively standardized ultrasound reports (presence of intracavitary fluid, presence and size of adnexal mass, volume of free fluid, endometrial thickness).

In conclusion, most cases of suspected EPs that are eligible for medical treatment do not have a definitive diagnosis. Preventing unintentional administration of MTX to early IUPs not seen on sonography can be achieved by delaying treatment until a more conclusive

diagnosis can be established. Comprehensive counseling prior to MTX administration in patients without definitive diagnosis of EP is therefore required.

References

1. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980–2007. *Obstet Gynecol* 2011; 117:837–843.
2. Tanaka T, Hayashi H, Kutsuzawa T, Fujimoto S, Ichinoe K. Treatment of interstitial ectopic pregnancy with methotrexate: report of a successful case. *Fertil Steril* 1982; 37:851–852.
3. Hoover KW, Tao G, Kent CK. Trends in the diagnosis and treatment of ectopic pregnancy in the United States. *Obstet Gynecol* 2010; 115:495–502.
4. Creinin MD, Washington AE. Cost of ectopic pregnancy management: surgery versus methotrexate. *Fertil Steril* 1993; 60:963–969.
5. Ailawadi M, Lorch SA, Barnhart KT. Cost-effectiveness of presumptively medically treating women at risk for ectopic pregnancy compared with first performing a dilatation and curettage. *Fertil Steril* 2005; 83:376–382.
6. Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. *Cochrane Database Syst Rev* 2007; 1:CD000324.
7. Banerjee S, Aslam N, Zosmer N, Woelfer B, Jurkovic D. The expectant management of women with pregnancies of unknown location. *Ultrasound Obstet Gynecol* 1999; 14:231–236.
8. Barnhart K, van Mello NM, Bourne T, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertil Steril* 2011; 95:857–866.
9. Condous G, Timmerman D, Goldstein S, Valentin L, Jurkovic D, Bourne T. Pregnancies of unknown location: consensus statement. *Ultrasound Obstet Gynecol* 2006; 28:121–122.
10. Barnhart KT, Katz I, Hummel A, Gracia CR. Presumed diagnosis of ectopic pregnancy. *Obstet Gynecol* 2002; 100:505–510.
11. Shaunik A, Kulp J, Appleby DH, Sammel MD, Barnhart KT. Utility of dilation and curettage in the diagnosis of pregnancy of unknown location. *Am J Obstet Gynecol* 2011; 204:130.e1–e6.
12. Alleyassin A, Khademi A, Aghahosseini M, Safdarian L, Badenoosh B, Hamed EA. Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: a prospective, randomized clinical trial. *Fertil Steril* 2006; 85:1661–1666.
13. Bonin L, Pedreiro C, Moret S, Chene G, Gaucherand P, Lamblin G. Predictive factors for the methotrexate treatment outcome in ectopic pregnancy: A comparative study of 400 cases. *Eur J Obstet Gynecol Reprod Biol* 2017; 208:23–30.
14. Nurmohamed L, Moretti ME, Schechter T, et al. Outcome following high-dose methotrexate in pregnancies misdiagnosed as ectopic. *Am J Obstet Gynecol* 2011; 205:533.e1–533.e3.
15. Addar MH. Methotrexate embryopathy in a surviving intrauterine fetus after presumed diagnosis of ectopic pregnancy: case report. *J Obstet Gynaecol Can* 2004; 26(11):1001–1003.
16. Usta IM, Nassar AH, Yunis KA, Abu-Musa AA. Methotrexate embryopathy after therapy for misdiagnosed ectopic pregnancy. *Int J Gynaecol Obstet* 2007; 99:253–255.
17. Poggi SH, Ghidini A. Importance of timing of gestational exposure to methotrexate for its teratogenic effects when used in setting of misdiagnosis of ectopic pregnancy. *Fertil Steril* 2011; 96:669–671.
18. Piggott KD, Sorbello A, Riddle E, DeCampli W. Congenital cardiac defects: a possible association of aminopterin syndrome and in utero methotrexate exposure? *Pediatr Cardiol* 2011; 32:518–520.
19. Bellin E, Fletcher DD, Geberer N, Islam S, Srivastava N. Democratizing information creation from health care data for quality improvement, research, and education—the Montefiore Medical Center experience. *Acad Med* 2010; 85:1362–1368.
20. Condous G, Van Calster B, Kirk E, et al. Clinical information does not improve the performance of mathematical models in predicting the outcome of pregnancies of unknown location. *Fertil Steril* 2007; 88(3):572–580.
21. Hertzberg BS, Kliewer MA, Bowie JD. Adnexal ring sign and hemoperitoneum caused by hemorrhagic ovarian cyst: pitfall in the sonographic diagnosis of ectopic pregnancy. *AJR Am J Roentgenol* 1999; 173:1301–1302.
22. Benson CB, Doubilet PM, Peters HE, Frates MC. Intrauterine fluid with ectopic pregnancy: a reappraisal. *J Ultrasound Med* 2013; 32:389–393.
23. Barnhart KT. Clinical practice. Ectopic pregnancy. *N Engl J Med* 2009; 361:379–387.
24. Levin I, Tsafrir Z, Sa'ar N, et al. "Watchful waiting" in ectopic pregnancies: a balance between reduced success rates and less methotrexate. *Fertil Steril* 2011; 95:1159–1160.
25. Jaspan D, Giraldo-Isaza M, Dandolu V, Cohen AW. Compliance with methotrexate therapy for presumed ectopic pregnancy in an inner-city population. *Fertil Steril* 2010; 94:1122–1124.
26. Dueñas-Garcia OF, Young C, Mikhail M, Salafia C. Compliance with follow-up in an inner-city population treated with intramuscular methotrexate for suspected ectopic pregnancy. *Int J Gynaecol Obstet* 2013; 120:254–256.
27. Abuhamad A, Minton KK, Benson CB, et al. Obstetric and gynecologic ultrasound curriculum and competency assessment in residency training programs: consensus report. *J Ultrasound Med* 2018; 37:19–50.