Clinical Policy: Critical Issues in the Initial Evaluation and Management of Patients Presenting to the Emergency Department in Early Pregnancy

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Approved by the ACEP Board of Directors April 10, 2012
Supported by the Emergency Nurses Association, June 21, 2012

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2012.04.021

[Ann Emerg Med. 2012;60:381-390.]

ABSTRACT

This clinical policy from the American College of Emergency Physicians is the revision of the 2003 Clinical Policy: Critical Issues in the Initial Evaluation and Management of Patients Presenting to the Emergency Department in Early Pregnancy.[1] A writing subcommittee reviewed the literature to derive evidence-based recommendations to help clinicians answer the following critical questions: (1) Should the emergency physician obtain a pelvic ultrasound in a clinically stable pregnant patient who presents to the emergency department (ED) with abdominal pain and/or vaginal bleeding and a beta human chorionic gonadotropin (β-hCG) level below a discriminatory threshold? (2) In patients who have an indeterminate transvaginal ultrasound, what is the diagnostic utility of β-hCG for predicting possible ectopic pregnancy? (3) In patients receiving methotrexate for confirmed or suspected ectopic pregnancy, what are the implications for ED management? Evidence was graded and recommendations were developed

based on the strength of the available data in the medical literature.

A literature search was also performed for a critical question from the 2003 clinical policy.[1] Is the administration of anti-D immunoglobulin indicated among Rh-negative women during the first trimester of pregnancy with threatened abortion, complete abortion, ectopic pregnancy, or minor abdominal trauma? Because no new, high-quality articles were found, the management recommendations from the previous policy are discussed in the introduction.

INTRODUCTION

Emergency physicians frequently evaluate and manage patients with abdominal pain and/or vaginal bleeding in the first trimester of pregnancy (also referred to here as "early pregnancy"). Their primary concern in this group of patients is to identify ectopic pregnancy. The prevalence of ectopic pregnancy in symptomatic emergency department (ED) patients is as high as 13% in some series, which is much higher than the prevalence in the general population.[2,3] With wide availability of bedside ultrasound in academic EDs and increasing access in community settings, more providers are now routinely using ultrasound in their evaluation of these patients.[4]

The term *bedside* ultrasound is used here to refer to pelvic ultrasounds that are performed in the ED by the emergency clinician, rather than in the radiology department. With the term *pelvic* ultrasound, the use of a transvaginal approach is implied unless transabdominal images have identified an intrauterine pregnancy. According to the 2006 ACEP policy statement *Emergency Ultrasound Imaging Criteria Compendium*, the primary indication for bedside ultrasound of the pelvis is to evaluate for the presence of intrauterine pregnancy, minimizing the likelihood of an ectopic pregnancy when modifying factors such as infertility treatment (putting patients at risk of heterotopic pregnancy) are not present.[5] A bedside ultrasonographer may or may not visualize the adnexa. A recent meta-analysis found that bedside ultrasound performed by emergency physicians can be used as a screening tool for ectopic pregnancy.[6] Pooled analysis included 10 studies and a total of 2,052 patients with 152 ectopic pregnancies; of those with ectopic pregnancy, 99.3% (95% confidence interval [CI] 96.6% to 100%) had no intrauterine pregnancy identified on bedside ultrasound.[6] A comprehensive ultrasound, in contrast, is usually performed in a radiology department and is expected to include views of the uterus, adnexa, and cul-de-sac. Studies using either or both categories of ultrasound were reviewed and this distinction was highlighted in the text and Evidentiary Table. This policy is not intended to review the evidence supporting the use of bedside ultrasound by emergency physicians.

Ultrasound has facilitated the evaluation of complications of early pregnancy; however, diagnostic algorithms still vary considerably among providers and institutions. Algorithms guiding the evaluation of abdominal pain or vaginal bleeding in early pregnancy generally incorporate the results of quantitative serum β-hCG measurements and pelvic ultrasonography. Many algorithms apply the principle of the discriminatory threshold,* historically defined as the level at which the sensitivity of ultrasound was thought to approach 100% for the detection of intrauterine pregnancy; the presumptive diagnosis of ectopic pregnancy is made if an intrauterine pregnancy is not visualized when the β-hCG is above a defined cutoff. This threshold depends on what ultrasound criteria are used to define an intrauterine pregnancy and is institution, operator, and patient dependent, but is commonly reported as ranging from 1,000 to 2,000 mIU/mL for radiologist-performed transvaginal sonography.[7,8] Although the traditionally defined discriminatory threshold is widely used, its applicability to ED practice is not as well established, and the concept itself has recently been called into question.[9,10] For these reasons, this policy refers to the general concept of a discriminatory threshold, where appropriate, but the discussion is not limited to any specific β-hCG cutoff.

The first critical question deals with the diagnostic and management variability that occurs when the clinician obtains a β-hCG result, and it is below a commonly defined discriminatory threshold. Some clinicians may not perform an ultrasound in these patients based on the incorrect assumption that an ectopic pregnancy is unlikely because the β-hCG level is low. In some settings, the emergency physician may be unable to obtain a comprehensive ultrasound in the radiology department for the same reason. However, it is well documented that ectopic pregnancies can present at almost any β-hCG level, high or low.[7] Some clinicians may defer an ultrasound when the β-hCG level is below the discriminatory threshold because they think that the risk of rupture is low. However, rupture has been documented at very low β-hCG levels.[7,11] Other clinicians may defer imaging in these cases because they believe that the diagnostic utility of pelvic ultrasound is low when the β-hCG level is below the discriminatory threshold or assume that there is little harm in delaying the diagnostic ultrasound.

The emergency physician is faced with another diagnostic and management question when an ultrasound is indeterminate, also called "nondiagnostic" or a "pregnancy of unknown location." The second critical question examines this subgroup of patients with indeterminate ultrasounds and addresses whether the initial β-hCG level can help risk-stratify these patients.

The third critical question explores the implications of methotrexate therapy for emergency medicine practice. Administration of methotrexate is an accepted and widely used alternative to laparoscopic surgery for the management of known or suspected ectopic pregnancy.[12-14] Methotrexate therapy is a complex intervention, and complications of therapy are frequently evaluated in the ED.

In the previous policy,[1] one of the critical questions also addressed the issue of which Rh-negative patients in the first trimester of pregnancy with threatened abortion, complete

*The discriminatory threshold is also referred to as the discriminatory zone or level.

abortion, ectopic pregnancy, or minor abdominal trauma required the administration of anti-D immunoglobulin. The level B recommendation was to administer 50 μg of anti-D immunoglobulin to Rh-negative women in all cases of documented first-trimester loss of established pregnancy to prevent Rh-D alloimmunization. There was insufficient evidence to recommend for or against its use in treating threatened abortion or ectopic pregnancy. There was also a level C recommendation to consider anti-D immunoglobulin use in cases of minor abdominal trauma. These recommendations were based on theoretic construct, multiple limited observational studies, and 1 limited randomized controlled trial. An updated literature search was performed on the topic, excluding abdominal trauma, and no high-quality studies were found addressing this issue. As a result, the patient management recommendations for this question remain unchanged and are not discussed in further detail in this policy update.

Recommendations from the 2003 clinical policy.[1]

Is the administration of anti-D immunoglobulin indicated among Rh-negative women during the first trimester of pregnancy with threatened abortion, complete abortion, ectopic pregnancy, or minor abdominal trauma?

Level A recommendations. None specified.

Level B recommendations. Administer 50 μg of anti-D immunoglobulin to Rh-negative women in all cases of documented first-trimester loss of established pregnancy.

Level C recommendations. Consider administration of anti-D immunoglobulin in cases of minor trauma in Rh-negative patients.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple searches of MEDLINE and Google Scholar were performed. All searches were limited to English-language sources and human studies. Specific key words/phrases and years used in the searches are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been described.[15] This policy is a product of the American College of Emergency Physicians (ACEP) clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, members of ACEP's Emergency Ultrasound Section, and individual members of the American College of Obstetricians and Gynecologists. Their responses were used to further refine and enhance this policy; however, their responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence. The articles were classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest design and design 3 representing the weakest design for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on dimensions related to the study's methodological features, including but not necessarily limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, external validity, generalizability, and sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula, taking into account the design and study quality (Appendix B). Articles identified with fatal flaws or that were not relevant to the critical question received an "X" grade and were not used in formulating recommendations for this policy. Grading was done with respect to the specific critical questions; thus, the level of evidence for any one study may vary according to the question. As such, it was possible for a single article to receive different levels of grading as different critical questions were answered from the same study. Question-specific level of evidence grading may be found in the Evidentiary Table (available online at http://www.annemergmed.com and at http://www.acep.org/clinicalpolicies/).

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on Class III studies, or in the absence of any adequate published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) were presented to help the reader better understand how the results may be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of patients with abdominal pain or vaginal bleeding in early pregnancy but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This guideline is intended for stable patients (with normal blood pressure and pulse rate) in the first trimester of pregnancy with abdominal pain or vaginal bleeding, without a previously confirmed intrauterine pregnancy.

Exclusion Criteria. This guideline is not intended to address the care of patients who are clinically unstable, have had abdominal trauma, or are at higher risk for heterotopic pregnancy such as those who are undergoing fertility treatments.

CRITICAL QUESTIONS

1. Should the emergency physician obtain a pelvic ultrasound in a clinically stable pregnant patient who presents to the ED with abdominal pain and/or vaginal bleeding and a β-hCG level below a discriminatory threshold?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Perform or obtain a pelvic ultrasound for symptomatic pregnant patients with a β-hCG level below any discriminatory threshold.

Key words/phrases for literature searches: ultrasound, β-hCG, transvaginal, ectopic pregnancy, pelvic pain, abdominal pain, vaginal bleeding, emergency department, and variations and combinations of the key words/phrases, years 1980 through September 2009.

Articles were reviewed for evidence of (1) the potential diagnostic benefit of performing an emergent bedside or comprehensive pelvic ultrasound in patients with abdominal pain and/or vaginal bleeding in early pregnancy and a β-hCG level below a discriminatory threshold, or (2) documented harm in deferring the ultrasound in this same group of patients. Assessing the safety of deferring a pelvic ultrasound, however, requires large numbers to detect the relatively rare event of a patient experiencing significant morbidity or mortality because of an ectopic pregnancy, and no study was large enough to confidently assess this risk. Furthermore, ED patients may have difficulty arranging appropriate follow-up; this fact is not reflected in the studies presented below but must be taken into account when deciding on the appropriate plan for any patient with a possible ectopic pregnancy. There was no attempt to compare the benefit of bedside versus comprehensive ultrasound for diagnostic performance, ED wait times, length of stay, or cost because this was beyond the scope of the question. However, when available, the use of bedside ultrasound may expedite the diagnosis.

Diagnostic benefit of performing a pelvic ultrasound in patients with a β-hCG level below a discriminatory threshold

The previous policy provided level C recommendations to consider transvaginal ultrasound in patients with a β-hCG level below 1,000 mIU/mL because it may detect intrauterine pregnancy or an ectopic pregnancy.[1] This was based on the moderate sensitivity of a comprehensive ultrasound for detecting intrauterine pregnancy (ranging from 40% to 67% across the studies), using presence of a "gestational sac" as the diagnostic criterion for intrauterine pregnancy, rather than a yolk sac or fetal pole.[8,16-18] Modest diagnostic performance of ultrasound in this group of patients with a β-hCG level below 1,000 mIU/mL was also observed for ectopic pregnancy, with a sensitivity of 19% and specificity of 100% in one series and a sensitivity of 39% in another study.[3,19]

In addition to the previously reviewed articles, 4 additional studies directly or indirectly address this question. A Class II study by Barnhart et al[20] examined the diagnostic performance of a comprehensive ultrasound in patients presenting to the ED with symptomatic early pregnancy and stratified the results by initial β-hCG level. For patients presenting with a β-hCG level below 1,500 mIU/mL, the sensitivity of ultrasound for the diagnosis of intrauterine pregnancy was 33% (95% CI 10% to 65%), and specificity was 98% (95% CI 90% to 100%). The sensitivity of ultrasound for the diagnosis of ectopic pregnancy was similar, at 25% (95% CI 5% to 57%), as was the specificity, at 96% (95% CI 87% to 99%).

Two Class III studies evaluated the diagnostic performance of a comprehensive ultrasound at presentation in patients who had the final diagnosis of ectopic pregnancy.[21,22] Cacciatore[21] conducted a review of the ultrasounds that he had performed. He found that ultrasound had 92% sensitivity for an ectopic pregnancy

with β-hCG level below 1,000 mIU/mL (95% CI 79% to 97%).[21] Counselman et al[22] found that among patients with a β-hCG below 1,000 mIU/mL, a comprehensive ultrasound was suggestive of an ectopic pregnancy in 86% (95% CI 60% to 96%) of cases that had the diagnosis confirmed.

One Class III study examined 74 patients with a bedside ultrasound result suggestive or diagnostic of an ectopic pregnancy, in which emergency physicians performed pelvic ultrasounds that included views of the uterus, adnexa, and cul-de-sac.[23] Of the 47 patients with a suggestive or diagnostic initial ultrasound result and a final diagnosis of an ectopic pregnancy, 36% had a presenting β-hCG level below 1,000 mIU/mL.

Potential harm of deferring pelvic ultrasound in patients with a β-hCG level below a discriminatory threshold

Algorithms that defer ultrasounds in stable patients with a β-hCG level below the discriminatory threshold may result in diagnostic delays. Unfortunately, the published studies do not allow us to estimate the risk of rupture or death among these patients. One Class III study reviewed the safety of a strategy of discharging symptomatic but stable, low-risk patients for urgent outpatient ultrasound within approximately 12 to 24 hours.[24] The authors retrospectively identified all patients who ultimately received a diagnosis of ectopic pregnancy. They found no adverse events, defined as death or need for fluid bolus because of hemodynamic instability, in 37 patients despite a median delay to ultrasound of 14 hours (range 0 to 126 hours), with 62% of patients waiting 12 hours or longer. The mean β-hCG level in this group was 2,887 mIU/mL (range 85 to 26,000 mIU/mL), but the number of patients with a β-hCG level less than the discriminatory threshold was not provided. The small number of patients in this study does not allow us to draw conclusions about the safety of delaying ultrasounds.

Another Class III study observed the performance of an algorithm that deferred ultrasounds in patients with an initial β-hCG level below 1,500 mIU/mL (until their β level plateaued or increased above this threshold).[7] For these 69 patients with a final diagnosis of an ectopic pregnancy, the authors found that mean time to diagnosis was 5.2 days.[7] There was no comparison group when ultrasound was performed immediately for patients with a β-hCG level below 1,500 mIU/mL. There were a small number of patients in this study with evidence of rupture at the time of diagnosis, but their initial β-hCG level was not provided, making the true risk of increased morbidity or mortality associated with this approach impossible to determine. However, some patients or clinicians might consider a delay in diagnosis unacceptable.

2. In patients who have an indeterminate transvaginal ultrasound, what is the diagnostic utility of β-hCG for predicting possible ectopic pregnancy?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Do not use the β-hCG value to exclude the diagnosis of ectopic pregnancy in patients who have an indeterminate ultrasound.

Level C recommendations. Obtain specialty consultation or arrange close outpatient follow-up for all patients with an indeterminate pelvic ultrasound.

Key words/phrases for literature searches: pelvic pain, abdominal pain, vaginal bleeding, ectopic pregnancy, β-hCG, transvaginal, ultrasound, emergency department, indeterminate ultrasound, pregnancy of unknown location, and variations and combinations of the key words/phrases, years 1980 through September 2009.

A majority of patients who have a pelvic ultrasound during their ED evaluation for symptomatic early pregnancy will receive a diagnosis of an intrauterine pregnancy or an abnormal pregnancy (eg, ectopic pregnancy, fetal demise, or molar pregnancy). A significant minority, however, will have an indeterminate, or nondiagnostic, ultrasound; most ED literature reports an indeterminate study rate of 20% to 30%.[3,9,25-28] This rate depends on a number of factors, including the clinical setting, patient population, ultrasound machine and operator, and criteria used for each diagnostic category. ED studies usually require the presence of a yolk sac or fetal pole to diagnose an intrauterine pregnancy. This is in contrast to diagnostic criteria more frequently used by radiologists, in which a "gestational sac" is diagnostic of intrauterine pregnancy if a "double decidual" sign is seen, even in the absence of a yolk sac or fetal pole. Diagnostic criteria for ectopic pregnancy vary as well, and some studies stratify findings into possible, probable, or definite ectopic pregnancy according to what is visualized in the adnexa or cul-de-sac. This can complicate comparisons among studies, and the definitions used in each study are noted in the Evidentiary Table (available online at http://www.annemergmed.com and at http://www.acep.org/clinicalpolicies/).

Indeterminate ultrasounds pose a management dilemma for the clinician. Authors for the ACEP 2003 clinical policy reviewed literature through 2000 to answer the related question, "Above what β-hCG level is the absence of intrauterine pregnancy by transvaginal ultrasound presumptive evidence of ectopic pregnancy?" and provided a Level B recommendation that patients with a indeterminate transvaginal ultrasound and a β-hCG level above 2,000 mIU/mL have follow-up arranged because they have a higher risk of ectopic pregnancy.[1] For this revision, the authors examined the broader question of whether the risk of ectopic pregnancy can be predicted in patients who have an indeterminate ultrasound with any β-hCG level and reported or calculated LRs from the available data to determine whether these could be applied to estimate a posttest risk of ectopic pregnancy that would be high or low enough to change management (Table). A positive test result was defined as an indeterminate ultrasound with a β-hCG level above a discriminatory threshold, and a negative test result as

an indeterminate ultrasound with a β-hCG level below a discriminatory threshold. Therefore, a positive LR estimates the risk of an ectopic pregnancy when the β-hCG level is above a discriminatory threshold, and a negative LR estimates the risk of an ectopic pregnancy when the β-hCG level is below a discriminatory threshold. When LRs were not available or could not be calculated, other statistical results were reported. Although not described in detail in the text, relative risk for ectopic pregnancy below a given β-hCG cutoff was also calculated (Table). The issue of serial β-hCG measurements is not addressed because this is not relevant to decisionmaking at the time of initial evaluation in the ED.

Nine Class II studies examined the initial β-hCG level in patients with an indeterminate ultrasound and found that it could not be used to predict final diagnosis.[3,9,26,27,29-33] Two reported on the performance of bedside ultrasounds.[9,27] The first study aimed to test the traditional concept of the discriminatory threshold in ED patients and found that using a β-hCG cutoff of 3,000 mIU/mL to try to predict which patients had an ectopic pregnancy had virtually no diagnostic utility (positive LR 0.8; negative LR 1.1).[9] The authors of the study also attempted to identify a more useful discriminatory threshold for bedside ultrasonography. Although there was no cutoff at which 100% of the intrauterine pregnancies were identified, a β-hCG level of more than 25,000 mIU/mL identified 88% (87 of 99 intrauterine pregnancies). The other study examining indeterminate bedside ultrasounds found that at the initial ED visit, median β-hCG level was not significantly different whether the final diagnosis was intrauterine pregnancy (1,304 mIU/mL), embryonic demise (1,572 mIU/mL), or ectopic pregnancy (1,147 mIU/mL) (P=NS).[27]

Six of the Class II studies examined indeterminate comprehensive ultrasounds.[3,26,29-32] Two studies of symptomatic ED patients from the same institution found that the negative LRs with a discriminatory threshold of 1,000 mIU/mL were not large or small enough to help with clinical decisionmaking.[3,26]

Four other Class II studies took place in an early pregnancy unit, which is a specialized evaluation center for patients with symptomatic or asymptomatic early pregnancy.[29-32] The first study examined several different common discriminatory thresholds for patients with indeterminate ultrasounds and found LRs close to 1 for discriminatory thresholds of 1,000 mIU/mL, 1,500 mIU/mL, and 2,000 mIU/mL.[29] Two studies by Condous et al[30,31] found that the mean initial β-hCG level for ectopic pregnancies was not significantly different than for the final diagnostic categories of intrauterine pregnancy or failing intrauterine pregnancy. The fourth study also found no significant difference in median initial β-hCG level regardless of the final diagnosis and reported that the receiver operating characteristic curve for β-hCG level is close to chance for predicting the need for intervention (area under the curve [AUC]=0.47; P=NS).[32]

The last Class II study examined indeterminate comprehensive ultrasounds performed by obstetricians and calculated LRs for different strata of β-hCG levels.[33] Data were extracted only for those patients without an ectopic mass or fluid in the pouch of Douglas. For β-hCG level above 1,000 mIU/mL, the positive LR was 3.1 and the negative LR was 0.7. When a β-hCG level above 2,000 mIU/mL was used as a cutoff, the positive LR was 25 and negative LR was 0.6. This is the single instance of a study yielding a strongly predictive positive LR.

Five Class III studies addressed this topic as well.[28,34-37] Two examined bedside ultrasound and 3, comprehensive ultrasounds. Four of these studies also found that β-hCG level was poorly predictive of ectopic pregnancy, based on LRs (Table).[28,34-36] A study examining expectant

β-hCG Threshold, mIU/mL	Study				Relative Risk of Ectopic Below Threshold* (95%CI)	Likelihood Ratios (95%CI)	
	Author	Year	Class	N		Negative†	Positive‡
1,000	Condous[29]	2005	II	527	0.6 (0.3–1.1)	0.9 (0.8–1.0)	1.7 (0.9–3.1)
	Dart[26]	2002	II	635	7.1 (3.4–14.9)	2.3 (1.9–2.7)	0.3 (0.2–0.5)
	Kaplan[3]	1996	II	72	3.8 (1.4–9.8)	2.5 (1.4–4.5)	0.5 (0.2–0.9)
	Mol[33]	1998	II	262	0.4 (0.2–0.5)	0.7 (0.5–0.8)	3.1 (2.0–4.8)
	Dart[36]	1998	III	220	2.2 (1.0–4.5)	1.8 (1.1–2.9)	0.7 (0.5–1.0)
1,500	Condous[29]	2005	II	527	0.4 (0.2–0.9)	0.9 (0.8–1.0)	2.3 (1.1–4.9)
2,000	Condous[29]	2005	II	527	0.5 (0.2–1.1)	0.9 (0.8–1.0)	2.3 (0.9–5.7)
	Mol[33]	1998	II	262	0.2 (0.1–0.3)	0.6 (0.5–0.8)	25 (7.9–81)
	Mateer[34]	1996	III	95	0.5 (0.3–0.8)	0.7 (0.5–0.9)	2.3 (1.2–4.3)
3,000	Wang[9]	2011	II	141	1.3 (0.6–2.6)	1.1 (0.8–1.5)	0.8 (0.5–1.4)
	Dart[35]	1997	III	194	2.1 (0.9–4.8)	1.4 (1.0–1.8)	0.6 (0.3–1.1)

*Relative risk was calculated with the online calculator http://ktclearinghouse.ca/cebm/practise/ca/calculators/statscalc.
†Negative LRs were determined based on having a β-hCG level below the stated threshold.
‡Positive LRs were determined based on having a β-hCG level above the stated threshold.

management of pregnancies of uncertain location found no significant difference in mean β-hCG level between ectopic pregnancy requiring treatment and other final outcomes.[37]

3. In patients receiving methotrexate for confirmed or, suspected ectopic pregnancy, what are the implications for ED management?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. (1) Arrange outpatient follow-up for patients who receive methotrexate therapy in the ED for a confirmed or suspected ectopic pregnancy.

(2) Strongly consider ruptured ectopic pregnancy in the differential diagnosis of patients who have received methotrexate and present with concerning signs or symptoms.

Level C recommendations. None specified.

Key words/phrases for literature searches: methotrexate, ectopic pregnancy, side effects, drug interactions, emergency service, and variations and combinations of the key words/phrases, years 2000 to May 2008.

Methotrexate administration in the ED is an alternative to surgical treatment for known or suspected early ectopic pregnancy.[12,13] The decision to administer methotrexate or use another treatment approach is complex. Methotrexate is given to hemodynamically stable patients with an unruptured ectopic pregnancy as a single intravenous or intramuscular dose of 50 mg/m^2, after which they are discharged to outpatient management.[14] Because treatment with a single dose of methotrexate is often ineffective, patients may require repeated doses of methotrexate until their β-hCG levels are clearly decreasing. Laboratory testing, including a CBC count with differential and platelet counts, hepatic enzyme level, and renal function tests, is recommended before initiation of methotrexate therapy.[14] Methotrexate therapy is contraindicated in patients with alcoholism, immunodeficiency, peptic ulcer, or active disease of the lungs, liver, kidneys, or hematopoietic system and relatively contraindicated in patients with an ectopic gestational sac larger than 3.5 cm or with embryonic cardiac motion observed on ultrasound.[14] Treatment success rates are also lower in patients who have a β-hCG level of 5,000 mIU/L or more.[13]

Treatment failure, with rupture of the ectopic pregnancy, is one of the most serious complications of methotrexate therapy. In several cohort studies, more than 20% of patients receiving methotrexate required surgery.[38-42] Therefore, ruptured ectopic pregnancy must be considered in the differential diagnosis of patients who present to the ED with concerning symptoms or signs after methotrexate therapy.

This section is an update of the 2003 policy[1] question examining the failure rate of methotrexate treatment and its implications for ED management. Nineteen Class I, II, and III studies are included for discussion below.[13,38-40,41-55] This review does not address complications associated with methotrexate administration directly into the ectopic pregnancy, a procedure that is generally performed in the operating room under ultrasound or laparoscopic guidance.

Two Class I studies were identified.[41,43] In Rozenberg et al,[41] 212 women with ectopic pregnancy received intramuscular methotrexate that was repeated as needed. This trial was remarkable for the high failure rate (22.9%) and for the low observed risk of tubal rupture (0.5%). In the second Class I study, 62 women were randomized to receive either intramuscular methotrexate, repeated as needed, or immediate laparoscopic surgery.[43] Among the 34 women randomized to methotrexate therapy, the treatment failure rate was 15% and the rupture rate was 9%.

A single Class II clinical trial by Korhonen et al[44] evaluated low-dose oral methotrexate therapy (12.5 mg total) for suspected ectopic pregnancy. Treatment failure occurred in 23% of patients. The rupture rate was not reported.

In the Class III studies, the treatment failure rates ranged from 3% to 29%.[13,38-40,45-55] Among studies that reported data about rupture, this serious complication occurred in 0.5% to 19% of women treated.[39,40,45-49,51-54] A Class III structured literature review also found that treatment with multiple-dose methotrexate was associated with a 7% failure rate.[55] The frequency of rupture was not reported, but 12% of patients required rehospitalization. More recent studies confirm earlier observations that treatment failure and ruptured ectopic pregnancy continue to be associated with larger ectopic pregnancies as measured by ultrasound, higher serum β-hCG levels, and visualized fetal cardiac activity.[13,40,49,52,53]

The only study to examine the need for surgery as the primary outcome was a Class III prospective observational study that included 177 women with ectopic pregnancies, 29 of whom had ruptured ectopic pregnancy prior to therapy.[42] Nineteen percent of the women with unruptured ectopic pregnancy and 38% of women with ruptured ectopic pregnancy required surgery.

Taken together, these data show that methotrexate therapy for known or suspected ectopic pregnancy is a useful but potentially complex treatment strategy. Although this therapy may be appropriately initiated in the ED, follow-up care is essential. Patients who develop increasing pain and/or signs of hemodynamic instability after methotrexate therapy should receive stabilizing care and prompt diagnostic studies, such as abdominal and pelvic ultrasonography, to establish or exclude the diagnosis of ruptured ectopic pregnancy.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

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Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Useless
1–5	0.5–1	Rarely of value, only minimally changes pretest probability
10	0.1	Worthwhile test, may be diagnostic if the result is concordant with pretest probability
20	0.05	Strong test, usually diagnostic
100	0.01	Very accurate test, almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reductionx100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Kaplan et al[3]	1996	Prospective observational; included patients with first-trimester abdominal pain or bleeding presenting to the ED	Objective of the study was to assess the utility of comprehensive ultrasound, β-hCG, and history and physical in the diagnosis of ectopic pregnancy in the ED; secondary objective was to calculate predictive value of β-hCG; ultrasound was not performed if patients had incomplete abortion by examination, were unstable, or if ultrasound was unavailable; patients with no ultrasound or indeterminate ultrasound were admitted for further evaluation and diagnosis	Ultrasounds were categorized as IUP if gestational sac with yolk sac or fetal pole present; diagnostic or suggestive of an ectopic pregnancy if an extrauterine gestation, adnexal saclike ring, or complex or cystic mass with or without cul-de-sac fluid were seen	72 of 403 (18%) had indeterminate ultrasound results; overall incidence of ectopic pregnancy 13%; of patients with indeterminate ultrasound, 15 (21%) ultimately received a diagnosis of ectopic pregnancy; risk of ectopic pregnancy with indeterminate ultrasound was 10/25 (40%) for β-hCG ≤1,000 mIU/mL, 5/47 (11%) for β-hCG >1,000 mIU/mL	9% lost to follow-up; small sample size of patients with β-hCG <1,000 mIU/mL or indeterminate ultrasound; patients receiving a diagnosis of IUP and discharged from the ED were not followed at home	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Barnhart et al[7]	1994	Prospective observational; included pregnant patients with abdominal pain or vaginal bleeding; excluded patients with hemodynamic instability, peritonitis, an open os suggestive of incomplete abortion, or a recent termination of pregnancy	Objectives of the study were to (1) determine the discriminatory threshold, (2) observe the performance of diagnostic algorithm in which patients with β-hCG level >1,500 mIU/mL had transvaginal ultrasound; if they had no IUP, they were taken to the operating room for laparoscopy or uterine curettage was performed; patients with β-hCG level <1,500 mIU/mL did not have transvaginal ultrasound but were discharged with 48-h follow-up, (3) review the characteristics of ectopic pregnancies diagnosed by above protocol	Final diagnoses were characterized as normal IUP, miscarriage, ectopic pregnancy, molar pregnancy, or lost to follow-up	The discriminatory zone, based on 68 consecutive transvaginal ultrasounds, was established to be 1,500–2,000 mIU/mL; 167 stable patients received a final diagnosis of ectopic pregnancy; 69 (41%) had a β-hCG level <1,500 mIU/mL and therefore had had ultrasound deferred; in this group, the mean time to diagnosis of ectopic pregnancy was 5.2 days	Transvaginal ultrasounds were performed by radiologists; the authors report that 5 of 85 patients not initially receiving a diagnosis of ectopic pregnancy had evidence of rupture at the time of diagnosis at follow-up, but it is not reported whether they had an ultrasound deferred because of an initial β-hCG level <1,500 mIU/mL	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Wang et al[9]	2011	Cross-sectional study; included stable first-trimester pregnant patients presenting to the ED with symptoms of abdominal pain, vaginal bleeding, or syncope	The objective of the study was to assess the clinical utility of the discriminatory zone of β-hCG level 3,000 mIU/mL in differentiating ectopic from normal pregnancy after indeterminate bedside pelvic ultrasonography	Bedside ultrasounds included views of the uterus, adnexa, and cul-de-sac; bedside ultrasounds were categorized as (1) IUP, based on positive yolk sac or fetal pole, (2) no IUP, (3) indeterminate; final diagnosis of IUP was determined by visualization of IUP (with yolk sac) by radiology ultrasound or at 8-week follow-up interview	141 of 256 (55%) did not have an IUP diagnosed on bedside ultrasound; overall ectopic incidence was 11% (29/256); test characteristics of discriminatory threshold of β-hCG level 3,000 mIU/mL: sensitivity was 35% (95% CI 18% to 54%), specificity was 58% (95% CI 48% to 67%), positive LR 0.82 (95% CI 0.48 to 1.40), negative LR 1.13 (95% CI 0.83 to 1.50); authors attempted to identify a better discriminatory threshold but found there was no cutoff at which 100% of the intrauterine pregnancies were visualized; using a cutoff of more than 25,000 mIU/mL identified 87 of 99 (88%)	Convenience sample missed 18% of eligible patients	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Lipscomb et al[13]	1999	Retrospective case series	Chart review (N=360) of patients with ectopic pregnancy treated with methotrexate (50 mg/m^2 IM), repeated weekly as needed	Resolution of ectopic pregnancy, based on β-hCG resolution and clinical follow-up	10 patients withdrew (2 cervical pregnancies, 8 elective); of the remainder, 320/350 (91%) had resolution without surgery; ruptures not reported	Treatment failure associated with higher β-hCG level at study entry	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Barnhart et al[20]	1999	Retrospective chart review; included consecutive pregnant patients with abdominal pain or vaginal bleeding presenting to the ED	Objective of the study was to compare the diagnostic accuracy of comprehensive transvaginal ultrasounds for diagnosing ectopic pregnancy or other complications of early pregnancy in patients with a β-hCG level below and above the discriminatory zone of 1,500 mIU/mL	Transvaginal ultrasound findings were defined as IUP ("definitive gestational sac"), spontaneous miscarriage ("impressions of incomplete or complete miscarriage"), ectopic pregnancy, or nondiagnostic; final diagnosis was categorized as IUP, ectopic pregnancy (with surgical confirmation), spontaneous miscarriage, or other	Included 333 patients, 269 with β-hCG level >1,500 mIU/mL and 64 with β-hCG level <1,500 mIU/mL; overall ectopic pregnancy incidence was 8%, but it was 25% in patients with β-hCG level <1,500 mIU/mL; diagnostic performance of transvaginal ultrasounds for IUPs in group with β-hCG level <1,500 mIU/mL: sensitivity 33% (95% CI 10% to 65%), specificity 98% (95% CI 90% to 100%); diagnostic performance of transvaginal ultrasounds for ectopic pregnancies in group with β-hCG level <1,500 mIU/mL: sensitivity 25% (95% CI 5% to 57%), specificity 96% (95% CI 87% to 99%)	Transvaginal ultrasounds performed by radiologists; a relatively small number of patients with a β-hCG level <1,500 mIU/mL resulted in wide CI around the estimates of sensitivity and specificity	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Cacciatore[21]	1990	Secondary analysis of prospectively collected data from previous study comparing transabdominal ultrasound and transvaginal ultrasound, which included 380 pregnant patients with abdominal pain or vaginal bleeding; this study analyzed subgroups with ectopic pregnancy diagnosed at surgery, who had initial β-hCG level available and ultrasound within 48 h of surgery	The objective of this study was to correlate transvaginal ultrasound findings with β-hCG in patients with proven ectopic pregnancy	Ultrasound was considered diagnostic of ectopic pregnancy if complex adnexal mass or gestational saclike adnexal ring was seen, separate from the ovaries; ultrasound was "nondiagnostic" if pelvic fluid alone was seen; absence of IUP with β-hCG level >1,000 mIU/mL was considered suggestive of ectopic pregnancy	120 patients were included in this analysis, 38 of whom had a β-hCG level <1,000 mIU/mL; 32% incidence of ectopic pregnancy among original cohort of 380 patients; transvaginal ultrasound was diagnostic in 92% (95% CI 79% to 97%) with β-hCG level <1,000 mIU/mL	Appears to be a hospital-based study that includes patients referred for evaluation of possible ectopic pregnancy, with a high ectopic pregnancy prevalence; ultrasounds were originally performed by the author, and it is not stated whether they were reviewed in a blinded fashion	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Counselman et al[22]	1998	Multicenter, retrospective chart review; included patients with the final diagnosis of ectopic pregnancy, who had an ultrasound and β-hCG testing at initial ED presentation; unstable patients were not excluded if they were stable enough for ultrasound (included patients with tachycardia, anemia, or orthostatic blood pressure)	The objective of the study was to determine whether patients with an initial β-hCG level <1,000 mIU/mL and who received a final diagnosis of ectopic pregnancy had evidence of ectopic pregnancy on comprehensive ultrasound during their initial visit	The outcome measure was a diagnostic performance of the initial comprehensive ultrasound for ectopic pregnancy; ultrasound was considered diagnostic of ectopic pregnancy if an extrauterine fetal pole with cardiac activity was identified and was considered suggestive if there was an empty uterus plus a complex adnexal mass and/or a moderate to large amount of pelvic fluid	64 patients with ectopic pregnancy were included, of whom 18 had a β-hCG level <1,000 mIU/mL; of these 18 patients, 16 had findings suggestive of ectopic pregnancy, but this included 4 patients with vital sign abnormalities; 12 of 14 stable patients with β-hCG level <1,000 mIU/mL had evidence of ectopic pregnancy on ultrasound	Presenting symptoms were not abstracted from the chart; likely had selection bias for higher-risk patients, because there was no protocol to guide who was getting ultrasound on initial visit	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Adhikari et al[23]	2007	Retrospective study; included patients with "first-trimester complications'' presenting to the ED who had transvaginal ultrasound suggestive or diagnostic of ectopic pregnancy; excluded patients with only a small amount of free fluid and an empty uterus with no other suggestive findings	Objective of the study was to describe ED diagnosis of ectopic pregnancy	Ultrasound categorized as definite (extrauterine gestation with yolk sac or fetal pole), probable (tubal ring, complex adnexal mass, or large echogenic free fluid), or possible ectopic (adnexal mass); final diagnosis determined by consulting obstetrics service	Included 74 patients; transvaginal ultrasound found definite ectopic in 6 patients (8%), probable in 28 (38%), and possible in 40 (54%); 47 (64%) of patients included received a final diagnosis of ectopic pregnancy;17 (36%) with a final diagnosis of ectopic pregnancy had a β-hCG level <1,000 mIU/mL	Does not specify that patients were stable; transvaginal ultrasounds performed by emergency physicians but included views of the adnexa and cul-de-sac, as well as the uterus	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Hendry and Naidoo[24]	2001	Retrospective review; included patients with surgically diagnosed ectopic pregnancy who had presented to the ED in stable condition, with complaint of abdominal pain and/or vaginal bleeding in the first trimester; excluded unstable patients, defined as having major risk factors for ectopic pregnancy, vital sign abnormalities, peritoneal signs, or adnexal mass on examination	The objective of the study was to determine whether stable patients with final diagnosis of ectopic pregnancy experienced an adverse event between presentation to the ED and outpatient ultrasound at 12 to 24 h	An adverse event was defined as death or hemodynamic instability requiring a fluid bolus	Of 117 total patients with ectopic pregnancy, 37 were stable and had deferred ultrasound; the median delay from presentation to ultrasound was 14 h, and the range was 0 to 126 h; 62% waited 12 h or longer, but only 2 waited longer than 24 h; no adverse events were identified in the clinically stable group during the interval between presentation and ultrasound (95% CI 0% to 14%)	Small number of stable patients (by their definition) makes safety difficult to establish; assumed complete follow-up based on absence of other hospitals within a 100-km radius; retrospective chart review, and if no fluid bolus was reported it was assumed not to have been needed	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Dart et al[26]	2002	Prospective, observational study; included pregnant patients with abdominal pain and vaginal bleeding who presented to an ED and who had an ultrasound result that was indeterminate	The purpose of this study was to determine whether indeterminate comprehensive ultrasound results could be subclassified to risk-stratify patients; a secondary objective was to examine the predictive value of β-hCG level for ectopic pregnancy within each subclass of indeterminate ultrasound results	Ultrasound was diagnostic of IUP if a gestational sac with yolk sac or fetal pole was seen; ultrasound was considered diagnostic or suggestive of an ectopic pregnancy if it showed an extrauterine sac with or without a fetal pole or yolk sac, a complex mass discrete from the ovary, or a large amount of fluid in the cul-de-sac; all other study results were considered indeterminate; indeterminate subclassifications were empty uterus, gestational sac, nonspecific fluid, abnormal sac, echogenic material; final diagnosis was determined by a combination of follow-up with diagnostic ultrasound, serial β-hCG level measurements, and pathology	780 identified but 145 lost to follow-up; 635 patients with indeterminate ultrasound results included in analysis; overall incidence of ectopic pregnancy 7% (46 of 635); ectopic pregnancy rate with β-hCG level <1,000 mIU/mL: 15% (95% CI 11% to 20%); ectopic pregnancy rate with β-hCG level >1,000 mIU/mL: 2% (95% CI 1% to 4%)	Large number lost to follow-up	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Tayal et al[27]	2004	Prospective, observational study; included consecutive patients presenting to the ED with first-trimester abdominal pain or vaginal bleeding who had an indeterminate transvaginal ultrasound	The objective of this study was to examine the outcome of patients with indeterminate bedside transvaginal ultrasound on initial ED visit	Bedside ultrasounds included views of the uterus, adnexa, and cul-de-sac; ultrasound diagnostic criteria: IUP defined as gestational sac with yolk sac or fetal pole; embryonic demise sac above a specific diameter without yolk sac or fetal pole; ectopic pregnancy defined as extrauterine gestational sac with chorionic ring, yolk sac, or fetal pole; indeterminate was all others, except molar pregnancies; final diagnoses were defined as follows: IUP based on appropriate increase of β-hCG level, follow-up ultrasound, or clinic visit; ectopic pregnancy based on surgery or pathology report, or follow-up after methotrexate; miscarriage based on decreasing β-hCG level	1,490 patients had transvaginal ultrasound, and 300 (20%) had indeterminate findings; overall ectopic pregnancy incidence 4.5%; in the indeterminate group, there was no difference in β-hCG level by final diagnosis: IUP 1,304 mIU/mL, embryonic demise 1,572 mIU/mL, ectopic pregnancy 1,147 mIU/mL (P=0.748); final diagnosis in patients with indeterminate ultrasound: IUP 29% (95% CI 24% to 34%), embryonic demise 53% (95% CI 47% to 58%), ectopic pregnancy 15% (95% CI 11% to 19%), unknown 3% (95% CI 1% to 5%)	May have included some patients with abnormal vital signs or peritoneal signs	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Mateer et al[28]	1995	Prospective observational study; convenience sample of pregnant patients >18 y of age presenting to the ED with abdominal pain, vaginal bleeding, orthostasis, adnexal tenderness, or risk factors for ectopic pregnancy; excluded patients with hypotension or beyond 16 weeks of gestation	The primary objective of this study was to evaluate the diagnostic accuracy of bedside transvaginal ultrasounds performed by emergency physicians	Transvaginal ultrasound diagnostic definitions: definite IUP required a gestational sac plus yolk sac or fetal pole *or* double decidual sign "plus thick concentric echogenic ring"; probable abnormal IUP if large sac seen without yolk sac or fetal pole; ectopic pregnancy required extrauterine gestational sac with yolk sac or fetal pole; "no definite IUP" was none of above; final diagnosis determined by telephone contact, clinic records, surgical records, pathology report, subsequent ultrasound, or labor and delivery records	41 patients had "no definite IUP" on transvaginal ultrasound; of these 5/11 (45%) with β-hCG level >2,000 mIU/mL had an ectopic pregnancy; 8/30 (27%) with β-hCG level <2,000 mIU/mL had an ectopic pregnancy	Did not include only symptomatic patients; diagnosis of ectopic pregnancy actually required an extrauterine yolk sac or fetal pole; there was no "probably ectopic pregnancy" category	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Condous et al[29]	2005	Secondary analysis of prospectively collected observational data; included symptomatic and asymptomatic stable patients presenting to an early pregnancy unit who had a pregnancy of unknown location after transvaginal ultrasound	The objective was to evaluate the utility of different discriminatory thresholds for predicting ectopic pregnancy (if a pregnancy of unknown location with a β-hCG level above the threshold was considered predictive of an ectopic pregnancy)	Pregnancy of unknown location was defined as no ultrasound signs of "intrauterine sac," no "adnexal mass thought to be an ectopic pregnancy," no hemoperitoneum on ultrasound, and no tissue within the uterus thought to be retained products of conception; final diagnosis was IUP (based on IUP on repeat ultrasound), ectopic pregnancy (at laparoscopy or on pathology), failing pregnancy of unknown location (based on no definitive ultrasound findings and decreasing β-hCG level), or persistent pregnancy of unknown location (no definitive ultrasound findings but β-hCG level failing to decrease); persistent pregnancies of unknown location were grouped with ectopic pregnancies in the results section	527 patients with pregnancy of unknown location were included in analysis; final diagnoses were failing pregnancy of unknown location 300 (57%), IUP 181 (34%), ectopic pregnancy or persistent pregnancy of unknown location 46 (9%); among patients with pregnancy of unknown location, sensitivity and specificity of various discriminatory thresholds, respectively, for ectopic pregnancy were 1,000 mIU/mL 22%, 87% 1,500 mIU/mL 15%, 93% 2,000 mIU/mL 11%, 95%; among patients with pregnancy of unknown location, the PPV and NPV of various discriminatory thresholds, respectively, for ectopic pregnancy were 1,000 mIU/mL 14%, 92% 1,500 mIU/mL 18%, 92% 2,000 mIU/mL 18%, 92%	Not an ED population; includes both symptomatic and asymptomatic (often high-risk) patients referred to the early pregnancy unit; only 75% were symptomatic	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Condous et al[30]	2004	Model derivation and prospective validation; included stable pregnant patients presenting to an early pregnancy unit with pain and with or without bleeding, poor obstetric history, or who were there to establish gestational age; only patients with pregnancy of unknown location on initial ultrasound were included	The purpose of this study was to develop a model to predict the outcome of pregnancies of unknown location using demographic and hormonal data	Pregnancy of unknown location was defined as no ultrasound signs of "intrauterine sac," no "adnexal mass thought to be an ectopic pregnancy," no hemoperitoneum on ultrasound, and no tissue within the uterus thought to be retained products of conception; final diagnosis was IUP (based on IUP on repeat ultrasound), ectopic pregnancy (at laparoscopy or on pathology), failing pregnancy of unknown location (based on low progesterone or decrease of β-hCG level to <5 mIU/mL), or persistent pregnancy of unknown location	189 patients with pregnancy of unknown location were used in the derivation phase and 199 in the validation phase; mean β-hCG level in derivation set (mIU/mL): IUP 781 (SD 1,323), failing IUP 595(SD 894), ectopic pregnancy 1,510 (SD 2,374); differences between ectopic pregnancy and IUP or failing IUP plus IUP were not significant; mean β-hCG level in test set (mIU/mL): IUP (38%) 640 (SD 643), failing IUP (55%) 287 (SD 457), ectopic pregnancy (6%) 567 (SD 446)	Not an ED population; includes both symptomatic and asymptomatic (often high-risk) patients referred to the early pregnancy unit; model did not incorporate simple initial β-hCG level because of poor predictive performance in the past	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Condous et al[31]	2005	Retrospective data used for derivation and prospective data used for validation of clinical decision rule; data were collected in an early pregnancy unit on stable pregnant patients with pain and with or without bleeding and poor obstetric history, or to establish gestational age; only patients with pregnancy of unknown location on initial ultrasound were included	The purpose of this study was to derive a model to distinguish high-risk pregnancies of unknown location (high-risk ectopic pregnancy requiring management) from low-risk pregnancies of unknown location (early IUP, resolving pregnancy of unknown location, or resolving ectopic pregnancy) on the basis of a single visit with transvaginal ultrasound and β-hCG and progesterone levels	Pregnancy of unknown location was defined as no ultrasound signs of "intrauterine sac," no "adnexal mass thought to be an ectopic pregnancy," no hemoperitoneum on ultrasound, and no tissue within the uterus thought to be retained products of conception; final diagnosis was IUP (based on IUP on repeat ultrasound), ectopic pregnancy (at laparoscopy or on pathology), failing pregnancy of unknown location (based on low progesterone level or decrease of β-hCG level to <5 mIU/mL), or persistent pregnancy of unknown location	200 patients with pregnancy of unknown location were included in the derivation data set, and the decision rule was tested on 318 consecutive patients with pregnancy of unknown location; mean β-hCG level (mIU/mL) by final diagnosis in prospective data set: ectopic pregnancy (5%) 649 (SD 719), IUP (36%) 619 (SD 564), failing pregnancy of unknown location (59%) 329 (SD 663)	Not an ED population; includes both symptomatic and asymptomatic (often high-risk) patients referred to the early pregnancy unit; included patient data from previous publication; only data from test set are presented here to minimize overlap with data from previous publication	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Banerjee et al[32]	2001	Prospective observational; included patients with "suspected complications of early pregnancy" referred to an early pregnancy unit who had pregnancy of unknown location; excluded patients who were unstable or had products of conception visible on examination	The objective of the study was to compare 2 multi-parameter models for predicting the final diagnosis (location) of pregnancies of unknown location	Pregnancy of unknown location was defined as patients who did not have IUP, retained products, or an ectopic pregnancy; it excluded patients with "sac-like structure in the uterus, adnexal mass thought to be ectopic pregnancy, or patients with hemoperitoneum"; final diagnosis was determined when an IUP with live embryo was seen on ultrasound, ectopic pregnancy was diagnosed laparoscopically and on pathology, or pregnancy resolved with β-hCG level decreasing to <20 mIU/mL ("spontaneous resolution")	113 of 2,114 (5%) patients received a diagnosis of pregnancy of unknown location on initial visit, and 104 with complete data were included; final diagnoses of pregnancies of unknown location: 72 (69%) spontaneous resolution, 23 (22%) normal IUP, 2 (2%) miscarriage, 7 (7%) ectopic pregnancy; there was no difference in mean initial β-hCG level among the final diagnoses (*P*=0.48): 320 mIU/mL (95% CI 93 to 847 mIU/mL) spontaneous resolution, 385 mIU/mL (95% CI 297 to 582 mIU/mL) normal IUP, 139 mIU/mL miscarriage, 811 mIU/mL (95% CI 542 to 1,025 mIU/mL) ectopic pregnancy; the ROC curve for β-hCG was not significantly better than chance for predicting the need for intervention in a pregnancy of unknown location (AUC 0.47; *P*=NS)	Not an ED population; includes both symptomatic and asymptomatic (often high-risk) patients referred to the early pregnancy unit; transvaginal ultrasounds performed in the early pregnancy unit	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Mol et al[33]	1998	Prospective observational; included stable, consecutive pregnant patients with suspected ectopic pregnancy with 1 or more of the following: abdominal pain or vaginal bleeding, 6-week ultrasound without an IUP, risk factors for ectopic pregnancy, or D&C without villi on pathology; excluded patients who had undergone IVF and who had a complete miscarriage clinically	The objective of this study was to determine the diagnostic accuracy of initial and repeat β-hCG-level measurements in patients with an indeterminate transvaginal ultrasound	Transvaginal ultrasound (performed by obstetricians and included views of the adnexa and cul-de-sac) was considered diagnostic of IUP when an "intrauterine gestational sac" was seen; ectopic pregnancy was diagnosed only in the presence of an extrauterine gestational sac with yolk sac or fetal pole; otherwise, the transvaginal ultrasound was considered indeterminate; final diagnostic categories: IUP (by ultrasound at 12 weeks or pathology in case of miscarriage), ectopic pregnancy (at laparoscopy), nonviable pregnancies (nonviable IUPs or β-hCG level that resolved)	354 patients had an indeterminate transvaginal ultrasound; 58 patients had an adnexal mass and 14 had free fluid, 20 had both findings but were included in the indeterminate category by their definition; LR for ectopic pregnancy in patients *without* adnexal mass or free fluid (stratified by β-hCG level, mIU/mL): <1,000 (n=36): 0.62 (95% CI 0.5 to 0.8) 1,000-1,499 (n=2): 0.31 (95% CI 0.1 to 1.3) 1,500-1,999 (n=1): 0.63 (95% CI 0.1 to 5) ≥2,000 (n=24): 19 (95% CI 6.8 to 52)	Patients included were not the usual ED population; they included 34 patients suspected of having ectopic pregnancy based on negative routine ultrasound results at 6 weeks and 14 patients with negative pathology results after D&C	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Mateer et al[34]	1996	Prospective observational study; convenience sample of stable patients >18 y of age presenting to the ED with abdominal pain, vaginal bleeding, orthostasis, adnexal tenderness, and/or risk factors for ectopic pregnancy; excluded patients beyond 16 weeks of gestation	The primary objective of this study was to evaluate whether bedside transvaginal ultrasound performed by emergency physicians reduced rates of missed or ruptured ectopic pregnancy compared with previous diagnostic approach	Transvaginal ultrasound criteria were definite IUP defined as gestational sac plus yolk sac or fetal pole or double decidual sign "plus thick concentric echogenic ring"; probable abnormal IUP if large sac seen without yolk sac or fetal pole; ectopic pregnancy required extrauterine gestational sac with yolk sac or fetal pole; "no definite IUP" was none of above; final diagnosis determined by clinic follow-up records, surgical records, pathology report, subsequent ultrasound, or labor and delivery records	95 patients had indeterminate transvaginal ultrasound ("no definite IUP"); rates of ectopic pregnancy by β-hCG level: 16/28 (57%) with β-hCG level >2,000 mIU/mL; 19/67 (28%) with β-hCG level <2,000 mIU/mL	Did not include only symptomatic patients; diagnosis of ectopic pregnancy actually required an extrauterine yolk sac or fetal pole, there was no "probably ectopic pregnancy" category; of patients in the "no definite IUP" group who received an ectopic pregnancy diagnosis, 18 (51%) had an abnormal adnexal mass or free fluid, which was significantly higher than in the IUP or abortion groups; significant ancillary findings including abnormal adnexal mass or abnormal free fluid "were discussed with obstetrics/ gynecology consultants"	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Dart et al[35]	1997	Retrospective chart review; included first-trimester pregnant patients with abdominal pain or vaginal bleeding and indeterminate ultrasound who had presented to an ED	Objective of the study was to determine whether absence of gestational sac and β-hCG level >3,000 mIU/mL and/or LMP >38 days ago excludes IUP; according to their usual protocol, if it was daytime, all patients had an ultrasound; if it was night, only patients with β-hCG level >1,000 mIU/mL had an ultrasound; patients who had an indeterminate ultrasound or a β-hCG level <1,000 mIU/mL who had no ultrasound were admitted for inpatient observation and evaluation	Indeterminate ultrasound was defined as "neither diagnostic of IUP nor suggestive of ectopic pregnancy"; gestational sac alone was not considered diagnostic of an IUP; final diagnosis of ectopic pregnancy was confirmed surgically	194 patients with indeterminate ultrasound were included; percentage of ectopic pregnancy stratified by β-hCG level: β-hCG level >3,000 mIU/mL and no gestational sac (n=74) 9%; β-hCG level >3,000 mIU/mL with gestational sac (n=11) 0%; β-hCG level <3,000 mIU/mL (n=109) 18%	22% of eligible patients were not included	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Dart and Howard[36]	1998	Retrospective review; included patients with first-trimester abdominal pain or vaginal bleeding who had an indeterminate transvaginal ultrasound and had presented to the ED; excluded patients without a final diagnosis	Primary objective of this study was to estimate risk of ectopic pregnancy for various findings on indeterminate ultrasound; according to their usual protocol, if it was daytime, all patients had an ultrasound; if it was night, only patients with β-hCG level >1,000 mIU/mL had an ultrasound; patients who had an indeterminate ultrasound were admitted for inpatient observation and evaluation	Indeterminate ultrasounds were categorized as empty uterus, anechoic intrauterine fluid, echogenic intrauterine material, abnormal gestational sac, gestational sac without yolk sac/fetal pole; ultrasound was considered suggestive of ectopic pregnancy with extrauterine sac with or without a fetal pole or yolk sac, a complex mass discrete from the ovary, moderate to large amount of anechoic fluid, any echogenic fluid; ultrasound with gestational sac plus yolk sac or fetal pole was diagnostic of IUP; final diagnosis of normal pregnancy was determined by ultrasound or at delivery, abnormal IUP determined at D&C or by β-hCG level decreasing to zero, and ectopic pregnancy was confirmed by laparoscopy and pathology	220 patients with indeterminate ultrasound were included; 32 (14%) of these patients had an ectopic pregnancy; 13/60 (22%) with β-hCG level <1,000 mIU/mL had ectopic pregnancy; 16/160 (10%) with β-hCG level >1,000 mIU/mL had ectopic pregnancy	No ultrasounds were performed at night on symptomatic patients with β-hCG level <1,000 mIU/mL, per department protocol; this may have contributed to lower number of patients in this group	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Hahlin et al[37]	1995	Prospective observational; included stable patients with a pregnancy of unknown location; excluded patients with signs of incomplete abortion	The objective was to evaluate expectant management of pregnancies of unknown location	Final outcomes were categorized as normal pregnancy, spontaneous resolution, or requiring active management for ectopic pregnancy or spontaneous abortion	80 patients had unclear pregnancy location;16 received a diagnosis of ectopic pregnancy because they required active therapy; mean β-hCG level by final outcome (mIU/mL): spontaneous resolution (n=45) 355 (SD 446), active therapy for ectopic pregnancy (n=16)722 (SD 622), active therapy for spontaneous abortion (n=7) 783 (SD 724), normal pregnancy (n=12) 408 (SD 352); pairwise comparison *P*=NS	45 had spontaneous resolution of the pregnancy of unknown location and may have included undiagnosed ectopic pregnancies not requiring management	III
Periti et al[38]	2004	Retrospective case series	N=49 women with ectopic pregnancy received intravenous methotrexate (100 mg)	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	35 (71%) had resolution without surgery;14 (29%) required surgery; no discussion of ruptures	Exclusions: β-hCG level >5,000 mIU/mL adnexal mass diameter >4 cm; gestational age >8 weeks	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Ransom et al[39]	1994	Retrospective case series	N=21 women with ectopic pregnancy who received methotrexate (50 mg/m^2) IM, repeated after day 7 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	15 (71%) had resolution without surgery; 6 (29%) required surgery including 4 (19%) with rupture, 4 with hemoperitoneum, and 2 with hemodynamic instability	Serum progesterone level >10 ng/mL may predict treatment failure (sensitivity 100%, specificity 54% in this series)	III
Tawfiq et al[40]	2000	Retrospective case series	N=60 women with ectopic pregnancy who received methotrexate (50 mg/m^2) IM, repeated as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	44 (73%) had resolution without surgery; 16 (27%) required surgery including 10 (17%) with rupture; 11 patients (19%) had nausea/vomiting but none had more significant adverse effects	Treatment failure was associated with β-hCG level ≥4,000 mIU/mL (retrospectively derived cutoff; sensitivity 85%, specificity 65%)	III
Rozenberg et al[41]	2003	Clinical trial, multicenter, double blinded	N=212 women with ectopic pregnancy who received methotrexate (50 mg/m^2) IM, repeated on day 7 as needed; in addition, 113 women received mifepristone (600 mg by mouth), whereas 99 women received placebo tablets	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	162 (76%) had resolution without surgery; 48 (23%) required surgery; 1 patient (0.5%) had rupture; in addition, 30% had gastritis, 7% had stomatitis, and 3% had reversible alopecia		I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Kumtepe and Kadanali[42]	2004	Prospective observational	N=117 women with ectopic pregnancy received IM methotrexate (50 mg/m^2), repeated on day 7 as needed; this group includes 88 patients with unruptured ectopic pregnancy and 29 hemodynamically stable patients with ruptured ectopic pregnancy	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	71 (81%) of the patients with unruptured ectopic pregnancy and 18 (62%) of the patients with ruptured ectopic pregnancy had resolution without surgery; 17 (19%) of the patients with unruptured ectopic pregnancy and 11 (38%) of the women with ruptured ectopic pregnancy required surgery, although the number of patients who developed tubal rupture and/or hemodynamic instability after receiving methotrexate is not well described; at least 3 patients treated with methotrexate developed significant hemoperitoneum		III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Sowter et al[43]	2001	Clinical trial, multicenter, unblinded	N=62 women with ectopic pregnancy who were randomized to receive methotrexate (50 mg/m^2) IM, repeated on day 7 and subsequently as needed (n=34), or laparoscopic surgery (n=28)	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	Of the 34 women randomized to methotrexate, 29 (85%) had resolution without surgery, 5 (15%) required surgery, and 3 (9%) had rupture; overall medical and psychosocial outcomes were slightly better in the methotrexate group	Exclusion criteria: β-hCG level ≥5,000 mIU/mL or adnexal mass ≥3.5 cm in diameter	I
Korhonen et al[44]	1996	Clinical trial	N=60 women with ectopic pregnancy were randomized to receive oral methotrexate (2.5 mg daily x5) or placebo	Resolution of ectopic pregnancy, based on β-hCG level resolution and serial ultrasonography	For each treatment arm (n=30), 23 (77%) had resolution without surgery and 7 (23%) required surgery; no discussion of ruptures	Treatment with very low-dose methotrexate (total 12.5 mg orally) did not affect the outcome of ectopic pregnancy	II
Stovall and Ling[45]	1993	Prospective observational	Women (N=120) with early ectopic pregnancy (≤3.5 cm in greatest dimension) received methotrexate (50 mg/m^2 IM), repeated on day 7 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	113 (94.1%) had resolution without surgery; 7 (5.8%) required surgery, all for rupture		III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Stika et al[46]	1996	Retrospective case series	Women (N=50) with early ectopic pregnancy (≤3.5 cm in greatest dimension) received methotrexate (50 mg/m^2 IM), repeated weekly as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	39 (78%) had resolution without surgery; 11 (22%) required surgery; ruptures not reported, but 3 patients (6%) had >250 mL hemoperitoneum noted on operative reports	Treatment failure associated with higher pretreatment β-hCG levels (1,662 versus 2,726 mIU/mL)	III
Lipscomb et al[47]	1998	Retrospective case series	Chart review (N=315) of patients with ectopic pregnancy treated with methotrexate (50 mg/m^2 IM), repeated weekly as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	6 patients withdrew for unstated reasons; of the remainder, 287/309 (92.9%) had resolution without surgery; 9 (2.9%) required surgery, including 5 (1.6%) with ruptures	Median and maximum time to rupture were 14 and 32 days, respectively	III
Kucera et al[48]	2000	Retrospective case series	N=60 women with ectopic pregnancy who received IM methotrexate (50 mg/m^2), repeated on day 7 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	47 (78%) had resolution without surgery; 13 (22%) required surgery; 4 (7%) ruptured, all of whom were hemodynamically unstable	Excluded women with β-hCG levels >5,000 mIU/mL or ectopic mass >5 cm in greatest dimension	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
El-Lamie et al[49]	2002	Prospective observational	Women with ectopic pregnancy (N=35) received 50 mg/m^2 IM methotrexate, repeated on days 7 and 14 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	33 (94%) had resolution without surgery; 2 (6%) required surgery; 1 (3%) ruptured; in addition, 7 (20%) were hospitalized because of pain	Treatment failure associated with adnexal mass >3.6 cm and/or β-hCG level >1,000 mIU/mL	III
Gamzu et al[50]	2002	Prospective observational	Women with ectopic pregnancy (N=56) received IM methotrexate (50 mg/m^2); the number of patients requiring a second injection was not reported	Resolution of ectopic pregnancy, based on β-hCG level resolution and serial ultrasonography	50 (89%) had resolution without surgery; 6 (11%) required surgery; no discussion of ruptures	Extension of a previous cohort study by the same authors (Gamzu et al, *Fertil Steril* 2002;77:761-765), adding 6 patients during 5 months; risk factors for treatment failure: β-hCG level ≥2,000 mIU/mL; identified ectopic mass on ultrasound; very limited discussion of safety	III
Alshimmiri et al[51]	2003	Prospective observational	Women with ectopic pregnancy (N=77) received methotrexate 50 mg/m^2 IM, repeated on day 7 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	73 (95%) had resolution without surgery; 4 (5%) required surgery for ruptured ectopic pregnancy; in addition, 5 (6%) were hospitalized because of pain		III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Bixby et al[52]	2005	Retrospective case series	Chart review (N=62) of patients with ectopic pregnancy treated with single-dose methotrexate (50 mg/m^2 IM), repeated on day 7 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	45 (73%) had resolution without surgery; 17 (27%) required surgery; ruptures not reported; failure was associated with higher serum β-hCG level or visualization of a yolk sac or fetal heart motion on transvaginal ultrasonography		III
Dilbaz et al[53]	2006	Prospective observational	Women with ectopic pregnancy (N=58) received 50 mg/m^2 IM methotrexate, repeated on day 7 as needed	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	49 (84%) had resolution without surgery; 9 (16%) required surgery because of ruptured ectopic	The presence of subchorionic tubal hematoma in the ectopic gestation, visualization of an embryo on ultrasonography, and β-hCG level ≥3,000 mIU/mL were associated with rupture	III
Tang et al[54]	2006	Retrospective case series	N=11 women with ectopic pregnancy (interstitial location only) treated with methotrexate (300 mg) IV	Resolution of ectopic pregnancy, based on β-hCG level resolution and clinical follow-up	10 (91%) had resolution without surgery; 1 (9%) required surgery for tubal rupture		III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/ Comments	Class
Barnhart et al[55]	2003	Structured literature review	Structured review of 76 articles (N=1,327 patients) of women with ectopic pregnancy treated with methotrexate	Resolution of ectopic pregnancy with medical management	Single-dose methotrexate: 940/1,067 (88.1%) resolution without surgery; multiple-dose methotrexate: 241/260 (92.7%) had resolution without surgery; frequency of rupture not reported; rehospitalization rate approximately 12%, similar between groups		III

AUC, area under the curve; *β-hCG*, beta human chorionic gonadotropin; *CI*, confidence interval; *D&C*, dilatation and curettage; *ED*, emergency department; *h*, hour; *IUP*, intrauterine pregnancy; *IV*, intravenous; *IVF*, in vitro fertilization; *IM*, intramuscular; *km*, kilometer; *LMP*, last menstrual period; *LR*, likelihood ratio; *mg*, milligram; *NPV*, negative predictive value; *PPV*, positive predictive value; *ROC*, receiver operating characteristic; *y*, year.