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

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is an update of the 2012 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 with abdominal pain and/or vaginal bleeding and a β-human chorionic gonadotropin (β-hCG) level below a discriminatory threshold? (2) In patients who have an indeterminate transvaginal ultrasound result, what is the diagnostic utility of β-hCG for predicting possible ectopic pregnancy?

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 incidence in the general population.[2,3]

Ultrasound is part of the usual workup for patients with symptomatic early pregnancy. A meta-analysis[4] and systematic review[5] both found that bedside ultrasound performed by emergency physicians can be used as a screening tool for ectopic pregnancy; however, a review of the evidence supporting this practice is beyond the scope of this policy. 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. In this clinical policy, the term *pelvic ultrasound* implies the use of a transvaginal approach unless transabdominal images have identified an intrauterine pregnancy. According to the 2014 American College of Emergency Physicians (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, thus minimizing the likelihood of an ectopic pregnancy when modifying factors such as infertility treatment (putting patients at risk of heterotopic pregnancy) are not present.[6] The multidisciplinary association the American Institute of Ultrasound in Medicine (AIUM) further specifies that the definitive diagnosis of an intrauterine pregnancy be based on visualizing an intrauterine gestational sac containing a yolk sac or embryo-fetus with cardiac activity.[7] A bedside ultrasonographer may or may not visualize the adnexa. 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 is highlighted in the text and Evidentiary Table.

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-human chorionic gonadotropin (β-hCG) measurements and pelvic ultrasonography. Many algorithms apply the principle of the discriminatory threshold that historically has been defined as the level at which the sensitivity of ultrasound is thought to approach 100% for the detection of intrauterine pregnancy for the presumptive diagnosis of ectopic pregnancy if an intrauterine pregnancy is not visualized when the β-hCG is above that defined cutoff. This threshold depends on the ultrasound criteria 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 transvaginal sonography performed in the radiology department.[8,9] Although the traditionally defined discriminatory threshold has been widely accepted, its applicability to ED practice is not as well established, and the concept itself has been called into question.[10,11] For these reasons, this policy refers to the term "discriminatory threshold" where necessary but does not endorse the concept or refer to any specific β-hCG cutoff level.

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 for these patients because of incorrect assumptions (eg, ectopic pregnancy is unlikely because the β-hCG level is low, because of a misunderstanding that the risk of rupture is low in this subgroup). However, it is well documented that ectopic pregnancies can present at almost any β-hCG level, high or low,[8] and rupture has been documented at very low β-hCG levels.[8,12] In addition, ultrasound determination of pregnancy location for symptomatic patients has been designated as a Centers for Medicare & Medicaid Services (CMS) Core Quality Measure, with few exclusions such as lack of ultrasound availability. A β-hCG level is not part of the inclusion or exclusion criteria for this CMS core measure.[13]

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

The 2012 version of this clinical policy explored the implications of methotrexate therapy for emergency medicine practice.[1] Administration of methotrexate is an accepted and widely used alternative to laparoscopic surgery for the management of known or suspected ectopic pregnancy.[14-16] Complications of methotrexate therapy are frequently evaluated in the ED. The recommendations on this topic from the 2012 version were to (1) arrange outpatient follow-up for patients who receive methotrexate therapy in the ED for a confirmed or suspected ectopic pregnancy; and (2) strongly consider ruptured ectopic pregnancy in the differential diagnosis of patients who have received methotrexate and present with concerning signs or symptoms (Level B recommendations).

An updated literature search was conducted on this topic: 39 articles were identified and zero articles were selected for further review. Key words/phrases for literature searches: methotrexate, ectopic pregnancy, pregnancy, drug therapy, hospital, emergency service, emergency department, emergency room and variations and combinations of the key words/phrases; years September 1, 2009, to search date of July 13, 2015. Given that no new high-quality studies addressing this issue were identified, the critical question was dropped from this update of the policy.

In the 2003 version of this clinical policy,[17] one of the critical questions addressed the issue of which Rh-negative patients in the first trimester of pregnancy with threatened abortion, complete 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.

In the 2003 version,[17] there was also a Level C recommendation to consider anti-D immunoglobulin use in cases of minor abdominal trauma in Rh-negative patients. These recommendations were based on multiple limited observational studies and 1 randomized controlled trial with substantial limitations. An updated literature search was performed on the topic, excluding abdominal trauma, and no new high-quality studies were found addressing this issue; as a result, the recommendations for this question were unchanged and were not discussed further in the 2012 version.[1] An updated literature search was again conducted for this policy: 63 articles were identified in the search results and zero articles were selected for further review. Key words/phrases for literature searches: first trimester pregnancy, anti-D immunoglobulin, Rh-negative blood, rhesus D antibody, Rh-HR blood group system, chorionic gonadotropin, beta subunit, and variations and combinations of the key words/phrases; years September 1, 2009, to search date of July 13, 2015. Given that no new research studies were identified that directly addressed this issue, the question was dropped from this version of the policy. However, a 2015 bulletin addressing this topic was published by the American College of Obstetricians and Gynecologists (ACOG) and recommends the use of Rh(D)-immune globulin in the first trimester immediately after surgical management of early pregnancy loss or within 72 hours of the diagnosis of early pregnancy loss with planned medical management or expectant management.[18]

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature and was based on a systematic review of the literature. Searches of MEDLINE, MEDLINE InProcess, Scopus, Web of Science, and the Cochrane Database were performed. All searches were limited to English-language sources and human studies. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question for questions 1 and 2 and in the "Introduction" section for the topics of methotrexate therapy and anti-D immunoglobulin administration. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the 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 individual emergency physicians, individual members of ACOG and AIUM, and members of ACEP's Ultrasound Section and Medical Legal Committee. Comments were received during a 60-day open comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site. The responses were used to further refine and enhance this policy; however, the responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for review and considered for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

All articles used in the formulation of this clinical policy were graded by at least 2 methodologists and assigned a Class of Evidence. Each article was assigned a design class with design 1 representing the strongest study design and subsequent design classes (ie, design 2 and design 3) representing respectively weaker study designs for therapeutic, diagnostic, or prognostic clinical reports, or meta-analyses (Appendix A). Articles were then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, and generalizability. Using a predetermined process related to the study's design, methodological quality, and applicability to the critical question, articles received a final Class of Evidence grade (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or that were ultimately not applicable to the critical question received a Class of Evidence grade "X" 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 for which it is being considered. As such, it was possible for a single article to receive different Classes of Evidence as different critical questions were answered from the same study. Question-specific Classes of Evidence grading may be found in the Evidentiary Table (available online at www.annemergmed.com).

Translation of Classes of Evidence to Recommendation Levels

Strength of recommendations regarding each critical question were made by subcommittee members using results from strength of evidence grading, expert opinion, and consensus among subcommittee members according to the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

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) are 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 presenting to the ED 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 adequate empirical data 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.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical 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 who have 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.

For potential benefits and harms of implementing the recommendations, see Appendix D.

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. Perform or obtain a pelvic ultrasound for symptomatic pregnant patients with any β-hCG level.

Level C recommendations. None specified.

Key words/phrases for literature searches: ultrasound, uterine hemorrhage/ultrasonography, abdominal pain/ultrasonography, β-hCG, transvaginal ultrasound, pelvic ultrasound, emergency department, emergency room, emergency service, hospital, hospital emergency service, pregnancy, chorionic gonadotropin, beta subunit, pregnancy complications, and variations and combinations of the key words/phrases; years September 1, 2009, to search date of July 13, 2015.

Study Selection: Two hundred thirty-five articles were identified in the search. Five articles were selected from the search results for further review, with zero new articles included for this critical question.

Articles were reviewed for evidence of (1) the potential diagnostic benefit of performing an emergent bedside or comprehensive pelvic ultrasound for patients with abdominal pain and/or vaginal bleeding in early pregnancy and a β-hCG level below any discriminatory threshold, or (2) documented harm in deferring the ultrasound in this same group of patients. Assessing the safety of deferring a pelvic ultrasound 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. Another consideration is that resources vary among EDs, and beside or radiology ultrasound may not always be available. On the other hand, arranging appropriate outpatient follow-up for imaging or consultation is challenging in many urban and rural settings. Therefore, health system constraints need to be taken into account when deciding on the optimal management plan for any patient with a possible ectopic pregnancy.

Diagnostic Benefit of Performing a Pelvic Ultrasound in Patients With a β-hCG Level Below Any Discriminatory Threshold

No new studies were identified that affected the recommendation made in the previous version of this policy,[1] however, the supporting evidence was reviewed again and the recommendation was raised to a Level B based on a preponderance of evidence from Class II and III studies indicating a moderate degree of clinical certainty. The 2003 policy provided a Level C recommendation 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.[17] 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, as is usual in most ED studies.[9,19-21] 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.[3,22]

The 2012 policy[1] described 4 additional studies in more detail. A Class II study by Barnhart et al[23] 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% confidence interval [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 a final diagnosis of ectopic pregnancy.[24,25] Cacciatore[24] 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%).[24] Counselman et al[25] found that among patients with a β-hCG level below 1,000 mIU/mL, a comprehensive ultrasound result 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.[26] 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 did 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.[27] 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 did 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).[8] For these 69 patients with a final diagnosis of an ectopic pregnancy, the authors found that mean time to diagnosis was 5.2 days.[8] There was no comparison group in which 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 may consider a delay in diagnosis unacceptable.

2. In patients who have an indeterminate transvaginal ultrasound result, 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 result.

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

Key words/phrases for literature searches: ectopic pregnancy, chorionic gonadotropin, beta subunit, ultrasonography, transvaginal ultrasound, pelvic ultrasound, ultrasound, emergency room, emergency department, hospital emergency service, pregnancy complications, pregnancy, and variations and combinations of the key words/phrases; years September 1, 2009, to search date of July 13, 2015.

Study Selection: Eighty-one articles were identified in the search. Six articles were selected from the search results for further review, with zero new articles included for this critical question.

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, molar pregnancy). A significant minority, however, will have an indeterminate (or nondiagnostic) ultrasound result; the ED literature commonly reports an indeterminate study rate of 20% to 30%.[3,10,28-31] This rate depends on multiple 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 frequently used by radiologists, in which a "gestational sac" is diagnostic of intrauterine pregnancy if a "double decidual" sign is visualized, 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.

Indeterminate ultrasounds pose a management dilemma for the clinician. Authors of the ACEP 2003 clinical policy reviewed literature to answer a 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 an indeterminate transvaginal ultrasound result and a β-hCG level above 2,000 mIU/mL have follow-up arranged because they have a higher risk of

ectopic pregnancy.[17] In the 2012 version of this policy,[1] the authors examined the broader question of whether the risk of ectopic pregnancy can be predicted in patients who have an indeterminate ultrasound result 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 result with a β-hCG level above a discriminatory threshold, and a negative test result as an indeterminate ultrasound result with a β-hCG level 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, the 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 decision making during the initial ED evaluation.

In the 2012 policy,[1] 9 Class II studies were described that examined the initial β-hCG level in patients with an indeterminate ultrasound result and found that it could not be used to predict final diagnosis.[3,10,29,30,32-36] There were no new studies identified for this updated version of the clinical policy; thus, the studies from the 2012 version[1] are reviewed again in this version. 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 predict which patients without an intrauterine pregnancy on bedside ultrasound had an ectopic pregnancy had virtually no diagnostic utility (positive LR 0.8; negative LR 1.1).[10] The other study examining indeterminate bedside ultrasound results 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).[30]

Six of the Class II studies examined indeterminate comprehensive ultrasounds results.[3,29,32-35] Two studies of symptomatic ED patients from the same institution found that the negative LRs with a discriminatory threshold of 1,000 mIU/mL did not help with clinical decision making.[3,29] Four of the Class II studies took place in an early pregnancy unit, which is a specialized evaluation center for patients with symptomatic or asymptomatic early pregnancy.[32-35] The first study examined several different common discriminatory thresholds for patients with indeterminate ultrasound results and found LRs close to 1 for discriminatory thresholds of 1,000, 1,500, and 2,000 mIU/mL.[32] Two studies by Condous et al[33,34] found that the mean initial β-hCG level for ectopic pregnancies was not significantly different from that 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 was close to chance for predicting the need for intervention (area under the curve=0.47; *P*=NS).[35]

The last Class II study examined results of indeterminate comprehensive ultrasounds performed by obstetricians and calculated LRs for different strata of β-hCG levels.[36] 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.

Table. Test characteristics of various β-hCG level thresholds for predicting ectopic pregnancy.

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[32]	2005	II	527	0.6 (0.3–1.1)	0.9 (0.8–1.0)	1.7 (0.9–3.1)
	Dart[29]	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[36]	1998	II	262	0.4 (0.2–0.5)	0.7 (0.5–0.8)	3.1 (2.0–4.8)
	Dart[39]	1998	III	220	2.2 (1.0–4.5)	1.8 (1.1–2.9)	0.7 (0.5–1.0)
1,500	Condous[32]	2005	II	527	0.4 (0.2–0.9)	0.9 (0.8–1.0)	2.3 (1.1–4.9)
2,000	Condous[32]	2005	II	527	0.5 (0.2–1.1)	0.9 (0.8–1.0)	2.3 (0.9–5.7)
	Mol[36]	1998	II	262	0.2 (0.1–0.3)	0.6 (0.5–0.8)	25 (7.9–81)
	Mateer[37]	1996	III	95	0.5 (0.3–0.8)	0.7 (0.5–0.9)	2.3 (1.2–4.3)
3,000	Wang[10]	2011	II	141	1.3 (0.6–2.6)	1.1 (0.8–1.5)	0.8 (0.5–1.4)
	Dart[38]	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.

Five Class III studies addressed this topic as well.[31,37-40] Two examined bedside ultrasound and 3 assessed the accuracy of comprehensive ultrasound results. Four of these studies also concluded that β-hCG level was poorly predictive of ectopic pregnancy.[31,37-39] A study examining expectant management of pregnancies of uncertain location found no significant difference in mean β-hCG level between ectopic pregnancy requiring treatment and other final outcomes.[40]

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 series	Case series

*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	Does not change pretest probability
1-5	0.5-1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	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 reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix D. Potential benefits and harms of implementing the recommendations.

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. Perform or obtain a pelvic ultrasound for symptomatic pregnant patients with any β-hCG level.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations: Improved patient safety by decreasing the risk of missing an ectopic pregnancy among patients with a low β-hCG value. In addition, the potential for earlier diagnosis of a viable intrauterine pregnancy in many patients will likely reduce the need for further follow-up testing for ectopic pregnancy.

Potential Harm of Implementing the Recommendations: Increased use of ultrasound with associated costs and increased ED length of stay for patients, as well as a potential increase in unnecessary specialty consultations for false-positive or equivocal ultrasound results.

2. In patients who have an indeterminate transvaginal ultrasound result, 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 result.

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

Potential Benefit of Implementing the Recommendations: Reduced risk of missing an ectopic pregnancy in patients with an indeterminate ultrasound result.

Potential Harm of Implementing the Recommendations: Additional resource use, including potential admissions and/or an increase in invasive management of patients without an ectopic pregnancy who have an indeterminate ultrasound result.

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Kaplan et al[3] (1996)	II	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 examination 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 results 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 observed	72 of 403 (18%) had indeterminate ultrasound results; overall incidence of ectopic pregnancy 13%; of patients with indeterminate ultrasound results, 15 (21%) ultimately received a diagnosis of ectopic pregnancy; risk of ectopic pregnancy with indeterminate ultrasound result was 10/25 (40%) for β-hCG $\leq$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 result; patients receiving a diagnosis of IUP and discharged from the ED were not followed at home

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Barnhart et al[8] (1994)	III	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 to 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 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 reported 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 was not reported whether they had an ultrasound deferred because of an initial β-hCG level <1,500 mIU/mL

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wang et al[10] (2011)	II	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 result; bedside ultrasounds included views of the uterus, adnexa, and cul-de-sac; bedside ultrasounds were categorized as IUP, based on positive yolk sac or fetal pole, no IUP, or indeterminate; final diagnosis of IUP was determined by visualization of IUP (with yolk sac) by radiology ultrasound or at 8-wk 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; sonographers were not blinded to the β-hCG level and it is unknown whether they incorporated the results of the β-hCG level into their decision-making

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Barnhart et al[23] (1999)	II	Retrospective chart review; included consecutive pregnant patients with abdominal pain or vaginal bleeding who presented 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 or 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Cacciatore[24] (1990)	III	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 observed, separate from the ovaries; ultrasound was "nondiagnostic" if pelvic fluid alone was observed; 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	Appeared to be a hospital-based study that included patients referred for evaluation of possible ectopic pregnancy, with a high ectopic pregnancy prevalence; ultrasounds were originally performed by the author, and it was not stated whether they were reviewed in a blinded fashion

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Counselman et al[25] (1998)	III	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 the 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 receiving ultrasound on initial visit

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Adhikari et al[26] (2007)	III	Retrospective study; included patients with "first-trimester complications" presenting to the ED who had transvaginal ultrasound results 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 was 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	Did 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Hendry and Naidoo[27] (2001)	III	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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Dart et al[29] (2002)	II	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 observed; 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, and 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Tayal et al[30] (2004)	II	Prospective, observational study; included consecutive patients presenting to the ED with first-trimester abdominal pain or vaginal bleeding who had an indeterminate transvaginal ultrasound result	The objective of this study was to examine the outcome of patients with indeterminate bedside transvaginal ultrasound result on initial ED visit; IUP defined as gestational sac with yolk sac or fetal pole; embryonic demise defined as 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=.75); 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Mateer et al[31] (1995)	III	Prospective observational study; convenience sample of pregnant patients >18 y and 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Condous et al[32] (2005)	II	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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Condous et al[33] (2004)	II	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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Condous et al[34] (2005)	II	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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Banerjee et al[35] (2001)	II	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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Mol et al[36] (1998)	II	Prospective observational; included stable, consecutive pregnant patients with suspected ectopic pregnancy with 1 or more of the following: abdominal pain or vaginal bleeding, 6-wk 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 wk 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 to 1,499 (n=2): 0.31 (95% CI 0.1 to 1.3), 1,500 to 1,999 (n=1): 0.63 (95% CI 0.1 to 5), $\geq$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 wk and 14 patients with negative pathology results after D&C

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Mateer et al[37] (1996)	III	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 wk 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 observed 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 results ("no definite IUP"); rates of ectopic pregnancy by β-hCG level: 16/28 (57%) with β-hCG level $\geq$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"

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Dart et al[38] (1997)	III	Retrospective chart review; included first-trimester pregnant patients with abdominal pain or vaginal bleeding and indeterminate ultrasound results 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 excluded 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 result or a β-hCG level <1,000 mIU/mL who had no ultrasound were admitted for inpatient observation and evaluation; indeterminate ultrasound result 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Dart and Howard[39] (1998)	III	Retrospective review; included patients with first-trimester abdominal pain or vaginal bleeding who had an indeterminate transvaginal ultrasound result 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 result were admitted for inpatient observation and evaluation; indeterminate ultrasound results 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 results were included; 32 (14%) of them 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

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Hahlin et al[40] (1995)	III	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

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; *IVF*, in vitro fertilization; *km*, kilometer; *LMP*, last menstrual period; *LR*, likelihood ratio; *NPV*, negative predictive value; *NS*, not significant; *PPV*, positive predictive value; *ROC*, receiver operating characteristic; *SD*, standard deviation; *wk*, week; *y*, year.