Does This Woman Have an Ectopic Pregnancy?
The Rational Clinical Examination Systematic Review

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CLINICAL SCENARIOS

Case 1

A 21-year-old college student with a remote history of 1 prior miscarriage presents with 2 days of vaginal spotting and lower abdominal discomfort. A urine pregnancy test at home showed a positive result. Her last menstrual period was approximately 5 weeks ago, and she has no risk factors for ectopic pregnancy (ie, history of ectopic pregnancy or pelvic infection, current intrauterine contraceptive device use, prior tubal or pelvic surgery). Her vital signs are normal, and a physical examination is unremarkable. There is no sign of either intrauterine pregnancy or ectopic pregnancy on transvaginal sonography, and a serum human chorionic gonadotropin (hCG) level is noted to be 1748 mIU/mL.

Case 2

A 36-year-old sales manager presents to the emergency department (ED) 7 weeks after her last menstrual period reporting 4 days of worsening abdominal pain and new-onset vaginal bleeding. Her heart rate is 112/min, and a blood pressure measurement of 104/52 mm Hg is below her baseline. She has involuntary guarding on abdominal examination, and a bimanual examination reveals cervical motion tenderness and a tender left adnexal mass.

CME available online at www.jamanetworkcme.com and questions on p 1732.

Importance The rapid identification and accurate diagnosis of women who may have an ectopic pregnancy is critically important for reducing the maternal morbidity and mortality associated with this condition.

Objective To systematically review the accuracy and precision of the patient history, clinical examination, readily available laboratory values, and sonography in the diagnosis of ectopic pregnancy in women with abdominal pain or vaginal bleeding during early pregnancy.

Data Sources We conducted MEDLINE and EMBASE searches for English-language articles from 1965 to December 2012 reporting on the diagnosis of ectopic pregnancy.

Study Selection The analysis included prospective studies of 100 or more pregnant women with abdominal pain or vaginal bleeding that evaluated patient history, physical examination, laboratory values, and sonography compared with a reference standard of either (1) direct surgical visualization of ectopic pregnancy or (2) clinical follow-up for all pregnancies to prove that ectopic pregnancy was not missed. Of 10 890 articles identified by the search, 14 studies with 12 101 patients met the inclusion criteria.

Data Extraction and Synthesis Two authors (J.R.C. and M.V.C.) independently extracted data and assessed the quality of each study. A third author (L.A.B.) resolved any discrepancies.

Results All components of the patient history had a positive likelihood ratio (LR+) less than 1.5. The presence of an adnexal mass in the absence of an intrauterine pregnancy on transvaginal sonography (LR+ 111; 95% CI, 12-1028; n=6885), and the physical examination findings of cervical motion tenderness (LR+ 4.9; 95% CI, 1.7-14; n=1435), an adnexal mass (LR+ 2.4; 95% CI, 1.6-3.7; n=1378), and adnexal tenderness (LR+ 1.9; 95% CI, 1.0-3.5; n=1435) all increase the likelihood of ectopic pregnancy. A lack of adnexal abnormalities on transvaginal sonography (negative LR [LR−] 0.12; 95% CI, 0.03-0.55; n=6885) decreases the likelihood of ectopic pregnancy. Existing studies do not establish a single serum human chorionic gonadotropin (hCG) level that is diagnostic of ectopic pregnancy.

Conclusions and Relevance Transvaginal sonography is the single best diagnostic modality for evaluating women with suspected ectopic pregnancy. The presence of abdominal pain or vaginal bleeding during early pregnancy should prompt a transvaginal sonogram and quantitative serum hCG testing.

There is no evidence of an intrauterine pregnancy on transvaginal sonography, but there is a complex-appearing adnexal mass and a moderate amount of pelvic fluid. Her serum hCG level is 3679 mIU/mL.

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WHY IS THIS QUESTION IMPORTANT?

Ectopic pregnancy typically represents implantation of a fertilized ovum (embryo) within the distal portion of the fallopian tube—the location of 93% to 97% of ectopic pregnancies.[1,2] Other ectopic sites of pregnancy implantation include the interstitial portion of the fallopian tube, prior cesarean scar, cervix, ovary, and abdomen.[1,2] Heterotopic pregnancy, the co-occurrence of an ectopic pregnancy and intrauterine pregnancy, has increased in incidence and occurs in 0.3% to 0.8% of the general population and 1% to 3% of women pregnant as a result of assisted reproduction.[3,4]

Studies of insurance and managed care databases indicate that the incidence of ectopic pregnancy as a subset of all pregnancies is as high as 2.6%.[5-8] Because an increasing number of ectopic pregnancies are treated medically in the ambulatory setting, prior estimates based on data from inpatient admissions likely underestimate the true incidence.[9,10] Ectopic pregnancy is the leading cause of first-trimester pregnancy-related death, responsible for up to 6% of maternal mortality during early gestation (Box).[9-11] The relatively low maternal case-fatality rate of 3.8 deaths per 10 000 ectopic pregnancies is secondary to improved diagnostic modalities, which allow for identification of ectopic pregnancy prior to fallopian tube rupture and fatal intraperitoneal hemorrhage[10,12] and the development of less invasive therapeutic options.[13,14]

The widespread use of serial serum hCG levels and advances in sonographic technology have allowed for earlier and more accurate diagnoses of ectopic pregnancy (Box).[7,13,14] In spite of these advances in diagnostic capabilities, between 8% and 31% of women presenting with pain or vaginal bleeding during early pregnancy will initially be diagnosed as having a pregnancy of unknown location (PUL)—a positive pregnancy test and lack of an identifiable intrauterine or ectopic pregnancy on transvaginal sonography.[15-18] Approximately 7% to 20% of these women initially diagnosed with PUL are

subsequently diagnosed with ectopic pregnancy, and 40% of patients with ectopic pregnancy have a delay in diagnosis beyond the initial visit.[19-22]

A number of risk factors, such as prior ectopic pregnancy and a history of pelvic inflammatory disease, have been associated with the development of tubal ectopic pregnancy, although risk factors are not always present (eAppendix 1 at http://www.jama.com).[23-26] The differential diagnosis in a patient with vaginal bleeding or lower abdominal or pelvic pain during during early pregnancy includes ectopic pregnancy, miscarriage or an intrauterine pregnancy with unexplained bleeding, trauma, acute appendicitis, ovarian torsion, hemorrhagic or ruptured ovarian or corpus luteum cyst, urinary calculus, and pelvic inflammatory disease.[27] Fewer than half of the women with an ectopic pregnancy have the classically described symptoms of abdominal pain and vaginal bleeding. In fact, these symptoms are more likely to indicate miscarriage.[28-30] Determining the historical factors, physical examination findings, and diagnostic tests that significantly affect the likelihood of ectopic pregnancy may facilitate an earlier diagnosis and result in reduced morbidity and mortality.

Pathophysiology

In tubal ectopic pregnancy, the limited vascular supply of the fallopian tube cannot sustain trophoblast growth, and hCG levels eventually plateau or fall.[13,14,31] Corpus luteum dysfunction results from the absence of appropriate hormonal signaling from the developing trophoblast, and serum progesterone levels may be low.[32-35]

Vaginal bleeding in women with an ectopic pregnancy occurs as a result of sloughing of decidualized endometrium.[31] The developing embryo may stop growing because of inadequate blood supply and support, and the ectopic pregnancy may spontaneously resolve, or it may persist, with trophoblast tissue continuing to grow and invade.[32,36] Invasion into the mucosa of the fallopian tube leads to tubal disten-

> **Box. Key Points: Ectopic Pregnancy**
> - Occurs in up to 2.6% of all pregnancies
> - Responsible for 6% of maternal deaths during early pregnancy
> - Should be ruled out in any pregnant woman with abdominal pain or vaginal bleeding
> - Diagnosed by (serial) serum human chorionic gonadotropin measurements and transvaginal sonography

sion and intraluminal bleeding that may pass into the peritoneal cavity or uterine cavity. If the ectopic pregnancy remains undiagnosed and untreated, the tube may rupture, causing hemorrhage into the peritoneal cavity with possible hypovolemia and shock.

Evaluation of PUL and Suspected Ectopic Pregnancy

The patient history, including an assessment for risk factors, and physical examination are the principal screening tools used by primary care physicians to evaluate a patient with possible ectopic pregnancy. All women of reproductive age with abdominal pain or vaginal bleeding should have a pregnancy test[13,27,37] because the accuracy of clinical diagnosis of early pregnancy is low.[38]

Patient History. The location, nature, and severity of pain with ectopic pregnancy may be pelvic or abdominal, unilateral or bilateral, localized or generalized, dull, sharp, cramping, intermittent or continuous. Colicky pain presents mainly in the hypogastric or iliac regions and is most likely due to small-volume intraperitoneal hemorrhage. Localized abdominal or pelvic pain is caused by acute distension of the fallopian tube at the site of trophoblast implantation. Tubal rupture is typically associated with a longer-lasting, more generalized pain due to hemoperitoneum,[39] but rupture may also be associated with a decrease in or resolution of pain altogether. Pain referred to the shoulder, indicating irritation of

the diaphragm from intraperitoneal blood, is a late sign.[13,27,30,37]

Vaginal bleeding may be small in volume (spotting) or equivalent to a menstrual period. The passage of tissue does not distinguish failing intrauterine from ectopic pregnancy and may simply represent a cast of endometrial tissue.[13,27,37,40]

Physical Examination. Hypovolemia, tachycardia, hypotension, diaphoresis, and shock are late signs that may indicate ruptured ectopic pregnancy with intraperitoneal hemorrhage, and patients with these findings should be treated emergently. Although it is less common for women to present with these signs due to improved diagnostic methods,[13,30] women with hemodynamic instability or peritoneal signs and positive pregnancy test results potentially have a ruptured ectopic pregnancy and should have prompt evaluation by a gynecological surgeon.

Women with ectopic pregnancy may have pelvic pain or tenderness, cervical motion tenderness, vaginal bleeding, an adnexal mass, tenderness on digital vaginal examination, and adnexal tenderness. During the vaginal speculum examination, an open cervical os or presence of tissue suggests miscarriage. An ectopic pregnancy may be felt as a small, round, tender, and mobile swelling lateral to the uterus corresponding to the location of the pain or where tenderness is elicited.[37,40,41] Although some experts are concerned about a small risk of ectopic pregnancy rupture from palpation, the risk is not supported with evidence from case series.

Laboratory Studies and Imaging. Refinements in the sensitivity of laboratory measures and improvements in sonographic technology have greatly changed the diagnostic approach to patients with suspected ectopic pregnancy, making both quantitative serum hCG testing and transvaginal sonography requisite during the evaluation of women with pain or vaginal bleeding during early gestation (eAppendix 2).[3,13]

The presence of a gestational sac with yolk sac or fetal pole within the uterine cavity on sonography indicates an intrauterine pregnancy and effectively rules out ectopic pregnancy, except in the unusual circumstance of heterotopic pregnancy.[14,42] Although abdominal sonography may diagnose intrauterine pregnancy, this modality does not adequately assess the adnexa, and for this reason, transvaginal sonography is preferred for the evaluation of suspected ectopic pregnancy (**FIGURE** and eFigures 1-3).[3,43] Furthermore, recent systematic reviews of ED physician–performed transvaginal sonography report sensitivities for the detection of ectopic pregnancy to be similar to that of studies performed by radiologists and sonogram technicians.[44,45]

A single serum hCG measurement indicates when an intrauterine pregnancy should be visualized by transvaginal sonography.[13,14,46,47] This "discriminatory hCG value or cutoff" has been reported to be between 1500 and 3000 mIU/mL, but the debate regarding the most appropriate clinical value continues (eAppendix 2).[13-15,46,47] In hemodynamically stable patients who are likely to follow up, serial quantitative hCG values are helpful in assessing the viability of a pregnancy.[13,14] By convention, hCG levels are drawn in 48-hour intervals, and 99% of symptomatic women with a viable pregnancy will exhibit at least an increase of 53% (ratio, 1.53) over that period of time.[29] Serum progesterone levels have been used as an adjunct for evaluating pregnancy viability but should not be used alone to determine pregnancy location (eAppendix 2).[32-35,48]

We reviewed the literature to identify clinical findings that could be used by emergency physicians and primary care providers in the initial evaluation of women with abdominal/pelvic pain or vaginal bleeding in early pregnancy who may have an ectopic pregnancy. Our focus was not on pregnant women with pelvic pain and hemodynamic collapse, for whom rapid gynecological evaluation and management will always be necessary.

METHODS
Search Strategy and Quality Assessment

MEDLINE and EMBASE searches for English-language articles from 1965 to December 2012 were performed using the strategy previously published in The Rational Clinical Examination series. Specifically, we sought to identify prospective studies of reproductive-age women with abdominal pain or vaginal bleeding during early pregnancy. The results of this literature search were intended to differentiate between intrauterine and ectopic pregnancy and thus to apply only to women proven to be pregnant and not to all women with abdominal or gynecological symptoms. The exploded MeSH headings were *ectopic pregnancy, diagnosis, physical examination, sensitivity* and *specificity, diagnostic tests, history taking,* and *Bayes' theorem.* The literature search resulted in 10 890 abstracts that were systematically reviewed by 2 authors (J.R.C. and M.V.C.).

Studies were included if the sample size was 100 or more; the study used a reference standard of surgical visualization, clinical follow-up, or both for all pregnancies to ensure that ectopic pregnancy was not missed; and the data could be organized into 2-by-2 contingency tables (eFigure 4). A threshold sample size of 100 was chosen empirically, recognizing that smaller sample sizes would potentially have too broad a confidence interval around the sensitivity from each study, also resulting in a wider random-effects summary for the summary measures. Narrative and systematic reviews, studies without proper control groups, retrospective studies, studies limited to ruptured ectopic pregnancies, studies with a primary focus other than ectopic pregnancy, studies focusing on the effectiveness of contraceptive devices, and studies involving assisted reproduction and in vitro fertilization were excluded. All studies that met the inclusion criteria underwent independent quality assessment by 2 authors (J.R.C. and M.V.C.) using the levels for the *Rational Clinical Examination* series adapted to ectopic pregnancy (eTable 1).[49] We ex-

cluded all level 4 and 5 studies. Any discrepancies regarding study inclusion or quality assessment were resolved via the opinion of a third author (L.A.B.).

Two authors (J.R.C. and M.V.C.) systematically collected data from the studies using an extraction form developed a priori. The goal of our review was to evaluate the clinical findings, widely available laboratory tests interpreted in the context of the clinical setting, coupled with transvaginal sonography performed by the bedside clinician as part of the clinical examination. Although some of the in-

cluded studies did not explicitly state the type of physician (ie, ED physician, gynecologist, or radiologist) performing the study, we elected to include these data in our analysis and evaluate for heterogeneity. Ultimately, 14 studies with 12 101 patients covering a variety of ectopic pregnancy diagnostic findings were included in the final analysis (**TABLE 1**).[20,22,41,50-60]

Statistical Methods

Sensitivity, specificity, and positive (LR+) and negative (LR−) likelihood ratios with corresponding 95% confi-

dence intervals were calculated for all findings. When any single cell in the 2-by-2 table was empty, we added 0.5 to each cell to calculate the LR and confidence interval.[61] To summarize the results, ranges are reported for findings that were available from only 2 studies. For findings evaluated in 3 studies, we report the random-effects univariate summary measures along with the I^2 value to express the degree of homogeneity (**TABLE 2**). Analyses were conducted using version 2.2.057 of Comprehensive MetaAnalysis (Biostat).

Figure. Transvaginal Sonographic Appearance of a Tubal Ectopic Pregnancy
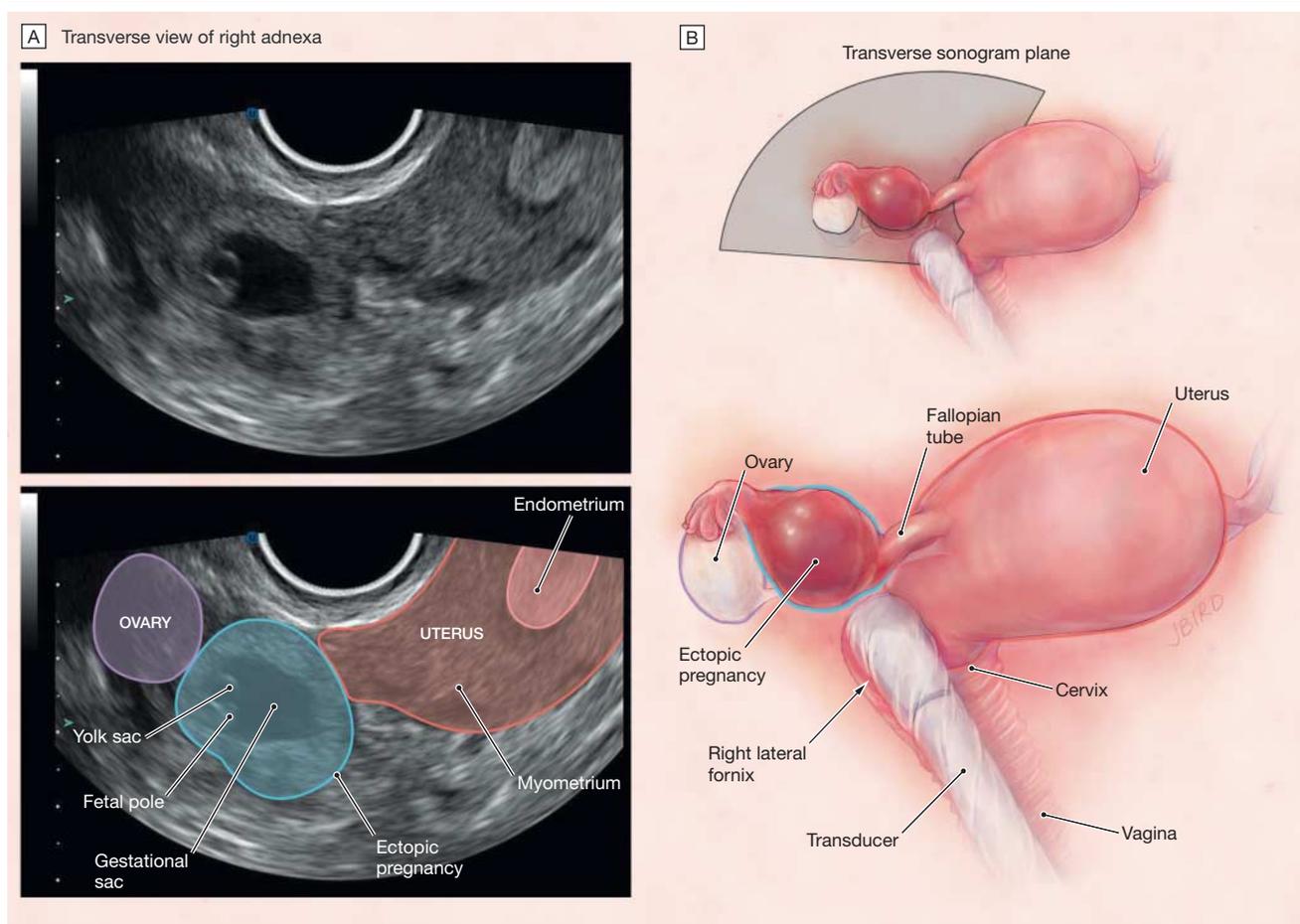
The transvaginal sonogram image was obtained in an asymptomatic woman 7 weeks and 4 days after her last menstrual period. A, The right tubal ectopic pregnancy can be seen in the transverse plane of the right adnexa as an echogenic ring (blue overlay) immediately lateral to the uterus (red overlay) and medial to the right ovary (purple overlay). A yolk sac and fetal pole can also be seen within the extrauterine gestational sac. The fetal pole was noted to measure 5.48 mm (6 weeks, 2 days) and a fetal heart rate of 123/min by M mode was detected (eFigures 1-3 at http://www.jama.com). B, The illustration shows the anteverted and anteflexed uterus (red outline) and transvaginal sonogram probe in the right lateral fornix. The sonographic plane of view (gray) is transverse and oblique through the right adnexa. The ectopic pregnancy (blue outline) is noted to be within the junction of the isthmic or ampullary portions of the right fallopian tube lateral to the uterus (red outline) and medial to the right ovary (purple outline).

RESULTS

There were 43 unique findings (eTable 2) reported in the 14 studies included in the final analysis (Table 1). Abdominal pain, vaginal bleeding, or a clinical suspicion of an ectopic pregnancy during early gestation were entrance criteria for all studies. All studies excluded women with evidence of hypovolemic shock. Among the studies determined to be level 1 or level 2 (n=10) by the quality assessment process, the summary prevalence of ectopic pregnancy among women with abdominal pain or vaginal bleeding was 15% (95% CI, 10%-22%; I^2=96%).

All components of the patient history and symptoms showed limited clinical value with all LR+ less than 1.5 (eTable 2). The presence of cervical motion tenderness during a digital vaginal examination (summary LR, 4.9; 95% CI, 1.7-14) or the finding of abdominal pain with cough or tender-

Table 1. Studies Included in Final Analysis

Study	Quality Assessment[49]	Sample Size, No.	Ectopic Pregnancies, No. (%)	Inclusion Criteria[a]	Findings Reported
Stovall et al,[22] 1990[b]	1	1994	161 (8)	LMP >25 d plus symptoms of pain (22%) or bleeding (28%) or other gynecological symptom	Patient history, physical examination, serum progesterone level
Florio et al,[56] 2007	1	536	76 (14)	Symptoms of pain (63%), bleeding (70%)	Patient history; levels of serum hCG, progesterone, and activin A
Buckley et al,[51] 1998[b]	1	486	39 (8)	Symptoms of pain (86%), bleeding (73%)	Patient history, physical examination
Kaplan et al,[20] 1996[b]	1	439	56 (13)	Symptoms of pain (89%), bleeding (70%)	Patient history, physical examination, TVS, serum hCG level
Mol et al,[41] 1999[b]	1	382	116 (30)	Clinical impression based on symptoms	Physical examination
Buckley et al,[52] 2000	1	317	22 (7)	Symptoms of pain or vaginal bleeding in first trimester	Serum progesterone level
Chambers et al,[53] 1990	2	267	53 (20)	Clinical impression based on symptoms	Abdominal sonography
Moore et al,[57] 2007	2	218	28 (13)	Symptoms of pain or vaginal bleeding in first trimester	Abdominal sonography
Timor-Tritsch et al,[59] 1989[b]	2	145	51 (35)	Clinical impression based on symptoms	TVS, abdominal sonography
Wang et al,[60] 2011	2	141	29 (21)	Symptoms of pain (82%), bleeding (65%)	TVS, serum hCG level
Condous et al,[54] 2005[b]	3	6621	143 (2)	Clinical impression based on symptoms	TVS
Ankum et al,[50] 1993[b]	3	208	89 (43)	Clinical impression based on symptoms	TVS
Norman et al,[58] 1988	3	175	95 (54)	Clinical impression based on symptoms	Urinary hCG level, serum hCG level
Dart et al,[55] 2002	3	172	24 (14)	Symptoms of pain or vaginal bleeding in first trimester	TVS, serum progesterone level

Abbreviations: hCG, human chorionic gonadotropin; LMP, last menstrual period; TVS, transvaginal sonography.
[a] Studies without incident rates of findings required the finding as an entrance criterion but did not report the frequency of the result.
[b] Included in the quantitative analysis.

Table 2. Summary Measures for Findings of Ectopic Pregnancy[a]

Finding	No. of Patients	Sensitivity	Specificity	LR+ (95% CI), I^2	LR− (95% CI), I^2
Physical examination					
Cervical motion tenderness[b]	1435[20,22,51]	0.45 (0.33-0.57)	0.91 (0.80-0.96)	4.9 (1.7-14), I^2 = 93%	0.62 (0.47-0.83), I^2 = 82%
Peritoneal findings[c]	868[41,51]	0.23-0.27	0.94-0.95	4.2-4.5	0.78-0.81
Adnexal mass[b]	1378[22,41,51]	0.09 (0.02-0.27)	0.96 (0.92-0.98)	2.4 (1.6-3.7), I^2 = 0	0.94 (0.87-1.0), I^2 = 79%
Adnexal tenderness[b]	1435[20,22,51]	0.61 (0.52-0.69)	0.65 (0.42-0.83)	1.9 (1.0-3.5), I^2 = 95%	0.57 (0.48-0.67) I^2 = 11%
Imaging					
Transvaginal sonography[d]	6885[50,54,59]	0.88 (0.52-0.98)	0.99 (0.96-1.0)	111 (12-1028), I^2 = 88%	0.12 (0.03-0.55), I^2 = 95%

Abbreviations: LR+, positive likelihood ratio; LR−, negative likelihood ratio.
[a] Random-effects univariate summary measures are shown for findings evaluated in 3 studies, with I^2 to express homogeneity. Ranges are shown for findings evaluated in only 2 studies. (See eTable 2 at http://www.jama.com for results from individual studies.)
[b] Detected during digital vaginal examination (bimanual palpation as part of pelvic examination).
[c] Abdominal pain on coughing or tenderness with light palpation.
[d] Studies evaluating transvaginal sonography only.

ness during light palpation (LR range, 4.2-4.5) were the most informative physical examination findings. The presence of an adnexal mass on bimanual examination also suggested ectopic pregnancy (summary LR, 2.4; 95% CI, 1.6-3.7). This finding exhibited the least heterogeneity across studies ($I^2=0$) and appeared to increase the likelihood of ectopic pregnancy more than adnexal tenderness (summary LR, 1.9; 95% CI, 1.0-3.5). Normal findings did not decrease the likelihood of an ectopic pregnancy, as the absence of cervical motion tenderness, peritoneal findings, an adnexal mass, or adnexal tenderness each had an LR greater than 0.5.

There is not a normal level or reference range for hCG, and a pregnancy location threshold for a single quantitative serum hCG level could not be established from the included studies.[20,56,60] Two studies that used thresholds of greater than 1000 mIU/mL or 3000 mIU/mL or greater were consistent with clinical practice where higher hCG values have been noted to be more consistent with a viable intrauterine pregnancy. This made an ectopic pregnancy less likely (LR range, 0.45-0.83 for values greater than the thresholds) (eTable 2).[20,60] A third study performed a receiver-operating-curve analysis and found the highest accuracy (0.75 sensitivity and 0.76 specificity) yielding an LR+ of 3.1 and LR− of 0.33 at a threshold of 658 mIU/mL.[56] Given the studies by Kaplan et al[20] and Wang et al,[60] however, the likelihood ratios were opposite of what was expected. Higher hCG levels had an LR of 3.1 (95% CI, 2.6-3.9), while values below the threshold had an LR of 0.33 (95% CI, 0.22-0.49). The majority (57%) of women in the study by Florio et al[56] had a spontaneous abortion, and all had hCG levels less than 658 mIU/mL. A reanalysis constrained to women with either an ectopic pregnancy or an intrauterine pregnancy showed that an hCG level of 1000 mIU/mL or greater had an LR of 1.8 (95% CI, 1.2-2.7) for an ectopic pregnancy, and an hCG level less than 1000 mIU/mL had an LR of 0.74 (95% CI, 0.60-0.92).

Transvaginal sonography was the single best diagnostic modality for detecting ectopic pregnancy. When the transvaginal sonogram indicated the presence of an adnexal mass and absence of an intrauterine pregnancy, the summary LR for an ectopic pregnancy was 111 (95% CI, 12-1028). Despite statistical heterogeneity ($I^2=88\%$), the results confirmed high clinical value even at the lower end of the confidence interval. The sensitivity of transvaginal sonography to detect ectopic pregnancy was 0.88 (95% CI, 0.52-0.98). The absence of adnexal findings had a summary LR of 0.12 (95% CI, 0.03-0.55; $I^2=95\%$) (Table 2).

DISCUSSION

To our knowledge, 2 prior systematic reviews previously investigated the use of ED physician–performed transvaginal sonography in the evaluation of suspected ectopic pregnancy.[44,45] The study by Stein et al[45] reports a pooled sensitivity of 0.99 (95% CI, 0.97-1.0) for the detection of ectopic pregnancy by transvaginal sonography. This is comparable with the sensitivity calculated in our study (0.88; 95% CI, 0.52-0.98), as well as others (0.73-0.93).[19,47,62,63] McRae et al[44] did not report pooled summary measures because of heterogeneity among the data. We also had statistical heterogeneity in the summary measures for transvaginal sonography and presume that this is due to including studies with transvaginal sonograms performed by various types of providers. Given the apparent high clinical value, even at the lower end of the confidence interval, we elected to present these data.

We did exclude 3 studies from our analysis that were included in both prior systematic reviews for the following reasons: all miscarriages were excluded from the study population,[64] there was no clear follow-up for all pregnancies,[65] and the study population was nonconsecutive.[66] Our analysis included 3 studies[50,54,59] not evaluated in either prior systematic review. Although there is no specific comment regarding the exclusion of these articles,

we presume that it is because these studies did not explicitly comment on who performed the sonograms.

SCENARIO RESOLUTION
Case 1

This patient is at approximately 5 weeks' gestational age with vaginal bleeding and abdominal pain. Although these symptoms are frequently seen in the setting of ectopic pregnancy, they are more likely to indicate either miscarriage or even an early, viable intrauterine pregnancy.[28-30,67] This patient does not report historical risk factors for ectopic pregnancy, but it is important to remember that more than half of women with ectopic pregnancy will have no identifiable risk factors.[30,40,68] Based on symptoms, her pretest probability of having an ectopic pregnancy is 15%. However, the highest-quality studies of consecutive patients suggested a broad confidence interval (10%-22%). Given the inability of history and physical examination findings to effectively rule out ectopic pregnancy, the most appropriate next diagnostic step is to obtain a transvaginal sonogram to evaluate for an intrauterine pregnancy.

The sonogram in this patient was equivocal, which is the case in 8% to 31% of women presenting in the first trimester with similar symptoms.[15-18] The sensitivity (0.88; 95% CI, 0.52-0.98) of transvaginal sonography for the detection of ectopic pregnancy calculated in our study agrees with those that have been previously reported (0.73-0.99).[19,45,47,62,63] The lack of adnexal findings on this patient's transvaginal sonography (summary LR, 0.12; 95% CI, 0.03-0.55) decreases the likelihood of ectopic pregnancy from a pretest probability of 15% to a posttest probability of 2%. Although the posttest probability of an ectopic pregnancy seems low in this patient, the broad confidence interval for the pretest probability and heterogeneity in the LR− may leave some uncertainty.

Her serum hCG level was 1748 mIU/mL. At this level, the presumption of ectopic pregnancy has a high false-positive rate,[13,14] and if a uterine curettage is performed, there is a significant possibility of interrupting a viable

pregnancy (eAppendix 2).[46,69-71] Given that the patient is hemodynamically stable with a low probability for ectopic pregnancy, the appropriate management is to repeat the hCG measurement in 48 hours. The clinician must reinforce the need for follow-up because adherence is poor among women undergoing conservative evaluation and management of ectopic pregnancy.[72] If a patient is at high risk for being lost to follow-up (ie, homeless, substance abusing, mentally ill, or socially at risk), consideration should be given to admission, aggressive social work, and outreach follow-up.

Case 2

In this patient, there is concern for hypovolemic shock secondary to intraperitoneal hemorrhage, as she has pelvic fluid on transvaginal sonography and is tachycardic and hypotensive. The physical examination findings of cervical motion tenderness (summary LR, 4.9; 95% CI, 1.7-14) and a mass in the left adnexa (summary LR, 2.4; 95% CI, 1.6-3.7) increase the likelihood of ectopic pregnancy. A transvaginal sonogram does indeed show a complex left adnexal mass (summary LR, 111; 95% CI, 12-1028), which we found to be the single most predictive finding for ectopic pregnancy. The serum hCG value (3679 mIU/mL) is also well above the level at which most experts agree the detection of an intrauterine pregnancy by transvaginal sonography would be expected (eAppendix 2).[13,14]

Given the symptoms, results of the transvaginal sonogram, and hCG level, her probability of ectopic pregnancy is high. The transvaginal sonogram findings alone increase the probability of an ectopic pregnancy to 95%. The concern for tubal rupture is also high in this scenario, and urgent gynecological evaluation should be requested while the patient is prepared for surgery.

CONCLUSIONS

Women with abdominal pain or vaginal bleeding during early pregnancy may have an ectopic pregnancy. This systematic review of the literature and meta-analysis confirms that the patient history and clinical examination alone are insufficient to indicate or eliminate the possibility of ectopic pregnancy. In a hemodynamically stable patient, the appropriate evaluation includes transvaginal sonography and quantitative (serial) serum hCG testing. Patients with signs and symptoms of excessive blood loss or hemodynamic collapse should immediately have gynecological evaluation.

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