CLINICAL PRACTICE

Beta-Human Chorionic Gonadotropin Levels and the Likelihood of Ectopic Pregnancy in Emergency Department Patients with Abdominal Pain or Vaginal Bleeding

Michael A. Kohn, MD, MPP, Kristi Kerr, MD, David Malkevich, MD, Nelda O'Neil, RN, M. James Kerr, MS, Beth C. Kaplan, MD

Abstract

Strategies for diagnosing ectopic pregnancy that defer endovaginal ultrasound in women with suggestive symptoms and serum beta-human chorionic gonadotropin (β-hCG) levels less than 1,500 mIU/mL ignore the increased risk of ectopic pregnancy in these patients. Objective: To quantify this increased risk by establishing and comparing the β-hCG distributions of symptomatic women with ectopic pregnancies, abnormal intrauterine pregnancies, and normal intrauterine pregnancies. Methods: The authors reviewed the records of a cohort of women who visited an urban emergency department (ED) during a 34-month period with abdominal pain or vaginal bleeding and nonzero quantitative β-hCG levels. Explicit criteria were used to determine whether the pregnancy ultimately turned out to be intrauterine and normal, intrauterine and abnormal, or ectopic. Probability distributions were compared using frequency distributions, receiver operating characteristic (ROC) curves, and likelihood ratios. Results: Of 730 ED patients included in the analysis, 96 (13%) had ectopic pregnancies, 253 (35%) had abnormal intrauterine pregnancies, and 381 (52%) had normal intrauterine pregnancies. The β-hCG distributions of patients with ectopic pregnancies and abnormal intrauterine pregnancies were similar and much lower than the β-hCG distribution of patients with normal intrauterine pregnancies. A β-hCG level less than 1,500 mIU/mL more than doubled the odds of ectopic pregnancy (likelihood ratio = 2.24). Of the 158 patients with β-hCG below 1,500 mIU/mL, 40 (25%; 95% confidence interval [CI] = 19% to 32%) had ectopic pregnancies, and only 25 (16%; CI = 11% to 22%) had normal intrauterine pregnancies. Conclusions: In women with pain or bleeding and serum β-hCG levels less than 1,500 mIU/mL, the risk of ectopic pregnancy is substantially increased, while the likelihood of normal intrauterine pregnancy is low. Key words: beta-human chorionic gonadotropin; ectopic pregnancy; likelihood ratios. ACADEMIC EMERGENCY MEDICINE 2003; 10:119–126.

When a woman of childbearing age presents to the emergency department (ED) with abdominal pain or vaginal bleeding, the diagnostic workup includes a history and physical examination (including a pelvic examination), a hematocrit, and a pregnancy test. If the pregnancy test is positive and the patient does not have an obviously gravid uterus or an open cervical os, the first concern is ectopic pregnancy.[1,2] Failing to identify an ectopic pregnancy in this situation can lead to delayed treatment, rupture, diminished fertility, hemorrhagic shock, even death.[1,2]

The two most common tests for ectopic pregnancy are the quantitative beta-human chorionic gonadotropin (β-hCG) and the endovaginal ultrasound. Until recently, substantial disagreement existed in the emergency medicine and obstetrics and gynecology literature about how to use these tests.[3–7] One reason for the disagreement was that this diagnostic problem does not fit the standard paradigm of a single dichotomous test for the presence or absence of a single disease. Even ignoring the possibility of molar and heterotopic pregnancies, we have to consider three pregnancy types: ectopic pregnancy, abnormal intrauterine pregnancy (spontaneous abortion), and normal (viable) intrauterine pregnancy. Instead of a dichotomous test, the β-hCG is a continuous measurement between 0 and 300,000 mIU/mL. Oversimplifying drastically, the ultrasound has at least three potential results: positive

From the Department of Epidemiology and Biostatistics (MAK), University of California, San Francisco, San Francisco, CA; the Department of Obstetrics and Gynecology (KK), Rex Hospital, Raleigh, NC; the Department of Emergency Medicine (DM), Plantation General Hospital, Plantation, FL; the Department of Emergency Services (NO, BCK), San Francisco General Hospital/ University of California, San Francisco, San Francisco, CA; and the Department of Chemistry (MJK), American University, Washington, DC.

Received June 18, 2002; revision received September 10, 2002; accepted September 10, 2002.

Presented at the SAEM annual meeting, St. Louis, MO, May 2002.

This work was carried out in part in the General Clinical Research Center at San Francisco General Hospital and supported by Grant 5-MO1-RR00083 from the Division of Research Resources, National Institutes of Health.

Address for correspondence and reprints: Michael A. Kohn, MD, MPP, P.O. Box 22, Millbrae, CA 94030. Fax: 650-692-5348; e-mail: mkohn@itsa.ucsf.edu.

for ectopic pregnancy, positive for intrauterine pregnancy, and indeterminate.

The β-hCG and the ultrasound are by no means independent tests. The ultrasound diagnosis of normal intrauterine pregnancy requires visualization of an intrauterine gestational sac with a yolk sac, which in normal pregnancy occurs at β-hCG levels of greater than about 1,500 to 2,500 mIU / mL.[8–10] The ultrasound's dependence on higher β-hCG levels to detect normal intrauterine pregnancy was widely acknowledged and incorporated into early diagnostic strategies that called for ultrasound only when the β-hCG exceeded a certain threshold.[11,12] These strategies assumed that the only way to diagnose an ectopic pregnancy was to demonstrate the absence of an intrauterine pregnancy when one should be visible. However, transvaginal ultrasound can also identify adnexal masses or free intraperitoneal fluid in ectopic pregnancies,[5] and ultrasound's sensitivity for these findings is less dependent on the level of β-hCG than its sensitivity for normal intrauterine pregnancy.[13] Ultrasound can also identify other findings, such as a 20-mm gestational sac without an embryo, consistent with abnormal intrauterine pregnancy. Even nondiagnostic ultrasounds can be useful by determining whether the uterus is empty or contains echogenic debris.[14] For these reasons, more recent diagnostic strategies call for transvaginal ultrasound as the first diagnostic procedure in women with abdominal pain or vaginal bleeding and positive urine pregnancy tests.[1,15–17]

Another argument against deferring transvaginal ultrasound in symptomatic women with below-threshold β-hCG levels is that they are at substantially higher risk for ectopic pregnancy. Since normal intrauterine pregnancies rarely cause pain or bleeding at below-threshold levels of β-hCG, women who present with pain or bleeding and low β-hCG levels are much more likely to have abnormal intrauterine or ectopic pregnancies. The goal of this study was to confirm and quantify this simple fact: that the probability of ectopic pregnancy in an ED patient with pain or bleeding increases as the level of β-hCG decreases. This quantification should be useful to clinicians who, for whatever reason, make clinical decisions based on a single β-hCG level without the benefit of a transvaginal ultrasound result.

METHODS

Study Design. This was a cohort study of pregnant women presenting to the San Francisco General Hospital Emergency Department for abdominal pain or vaginal bleeding. The study's objective was to determine how β-hCG level was associated with pregnancy type. We obtained approval from the Committee on Human Research of the University of California, San Francisco (including waiver of informed consent).

Study Setting and Population. The San Francisco General Emergency Department is an urban, public hospital ED that maintains a computer database of all visits. By cross-referencing this database of visits with a separate database of laboratory results, we were able to identify all visits between September 1, 1996, and June 30, 1999, by women who had a non-zero quantitative β-hCG (Third International Reference Preparation). We then reviewed the records of these women to determine whether they had symptoms suggestive of ectopic pregnancy as well as the outcomes of their pregnancies.

During the study period, the standard procedure for evaluating a woman with abdominal pain or vaginal bleeding, and a positive urine pregnancy test, was to obtain both a quantitative β-hCG and a pelvic ultrasound. If transabdominal ultrasound was nondiagnostic, the patient received a transvaginal ultrasound. If a formal ultrasound was available from the radiology department, it was obtained. Otherwise, the ultrasound was performed by the obstetrics / gynecology resident on call. During the study period, the emergency physicians were not performing ultrasounds. Any equivocal ultrasounds by the obstetrics / gynecology resident were followed by a formal radiology ultrasound when it became available. Generally, the β-hCG had already returned by the time of the ultrasound, unless the patient was unstable.

Study Protocol. We endeavored to adhere to the principles of a good chart review as outlined by Gilbert et al.[18] All authors except BCK participated in chart abstraction using a computerized form that incorporated the exclusion and outcome-classification criteria listed in Table 1. The computerized form included prompts to remind the abstractor of exclusion and outcome classification criteria. For example, if the abstractor coded ''abnormal intrauterine pregnancy'' as the outcome, the abstractor was required to identify which one of the criteria for abnormal intrauterine pregnancy was satisfied (Table 1). An initial abstractor training session introduced the abstractors to the computerized form, and meetings were held periodically to discuss problems and clarify criteria. The direct entry of chart abstraction data into a computer database enabled continuous monitoring of abstractors' progress, exclusion rates, and outcome classification rates. Although we could not completely blind the chart abstractors (who were assessing pregnancy outcome) to the predictor variable, β-hCG level, we did nothing to draw their attention to the β-hCG level or lead them to consider it in their determination of outcome.

All five abstractors independently reviewed a random sample of 50 charts, with oversampling of patients who were classified by the hospital's administrative coders as having ectopic pregnancies. The study exclusion criteria (Table 1) were intended to ensure that patients had presented with abdominal

TABLE 1. Inclusion, Exclusion, and Outcome Classification Criteria

Inclusion Criteria:
1. Presented to emergency department between 9/1/96 and 6/30/99
2. Non-zero quantitative beta-human chorionic gonadotropin (β-hCG)

Exclusion Criteria:
1. Chief complaint at triage was neither abdominal pain nor vaginal bleeding
2. Pregnancy location was known by prior ultrasound
3. Uterus was obviously gravid with fetal heart tones
4. Cervical os was open, consistent with a spontaneous abortion in progress or the patient brought in passed tissue
5. Patient had an evacuation procedure prior to the visit

Outcome Classification Criteria:
Ruptured Ectopic Pregnancy
1. Laparoscopy findings
2. Laparotomy findings

Unruptured Ectopic Pregnancy
1. Laparoscopy findings
2. Laparotomy findings
3. Ultrasound showing adnexal gestational sac and no or minimal pelvic fluid

Abnormal Intrauterine Pregnancy
1. Ultrasound showing gestational sac > 12 mm without a yolk sac
2. Ultrasound showing gestational sac > 20 mm without an embryo
3. Ultrasound showing an embryo without cardiac activity
4. Spontaneous abortion with fetal tissue documented histologically
5. Spontaneous abortion with fetal tissue documented clinically
6. Serial β-hCG measurements fell to zero spontaneously

Normal Intrauterine Pregnancy
1. Documented progression beyond the first trimester
2. Ultrasound showing embryo with cardiac activity
3. Ultrasound showing gestational sac with yolk sac, too early for cardiac activity

Intrauterine Pregnancy, Unknown if Abnormal or Normal
1. Uterine evacuation without prior ultrasound, fetal tissue by histology
2. Uterine evacuation without prior ultrasound, no tissue by histology, but β-hCG decreased to zero

pain or vaginal bleeding and were at risk for ectopic pregnancy. We determined the inter-rater reliability of study exclusion by having four of the abstracters reach consensus regarding the 50 shared charts and then comparing to the fifth abstractor. The kappa for study exclusion was 0.67. The four main diagnostic categories were normal intrauterine pregnancy, abnormal intrauterine pregnancy, ectopic pregnancy, and unknown. We determined the inter-rater reliability of these classifications on the 25 of 50 shared charts that all five abstractors included in the study. First, three abstractors reviewed these charts, discussed them, and reached consensus on diagnostic classification. These consensus classifications were compared with the independent classifications of the fourth and fifth abstractors. The unweighted kappa for three raters and four ratings was 0.84. All three raters agreed on 21 of the 25 shared charts, including all nine in which any rater coded an ectopic pregnancy.

Data Analysis. We determined and graphed the β-hCG frequency distributions for all three pregnancy types: normal intrauterine, abnormal intrauterine, and ectopic. Choosing β-hCG intervals for these frequency distributions was somewhat complicated. In early normal pregnancy, β-hCG increases logarithmically[19–22]; it is common to speak in terms of β-hCG doubling times[23–25]; and initial β-hCG concentrations are roughly normally distributed on a log scale.[16] However, at the upper end of the β-hCG distribution for normal intrauterine pregnancy, the distribution is skewed unless plotted on an arithmetic scale. For these reasons, we plotted the β-hCG frequency distributions on a modified log scale with each interval corresponding roughly to a β-hCG doubling time except at the upper end of the scale (β-hCG > 100,000 mIU/mL) where the scale is arithmetic with intervals of 50,000 mIU/mL. Intervals are not exact doubles of each other, because the cutoffs of 1,500 and 40,000 mIU/mL were essential for comparison with other studies.[6,12,26] The geometric means of the three groups were compared using analysis of variance (ANOVA), with pair-wise comparisons using the Scheffe correction (Stata, College Station, TX). The frequency distributions were also used to calculate likelihood ratios and plot receiver operating characteristic (ROC) curves.

For comparison with other studies,[6,12,26] we also broke the continuous range of β-hCG values into three intervals: <1,500 mIU/mL, 1,500–39,999 mIU/mL, and ≥40,000 mIU/mL. For each pregnancy type, the probability of a β-hCG value in these three intervals

was calculated. This enabled the calculation of likelihood ratios for ectopic pregnancy, as against abnormal or normal intrauterine pregnancy, for each of these three β-hCG intervals. We calculated likelihood ratios in addition to prevalences (predictive values) to separate the diagnostic value of the β-hCG level from the overall prevalence of ectopic pregnancy in our population.

RESULTS

Of 1,218 visits by women with non-zero serum β-hCG measurements, 373 (31%) were excluded based on the criteria in Table 1 (mainly because the patients did not have pain or bleeding, or they had clear-cut clinical diagnoses of spontaneous abortion); 66 did not have the location of the pregnancy established; and 49 had intrauterine pregnancies that could not be classified as normal or abnormal. This left 730 visits for abdominal pain or vaginal bleeding in which the type of pregnancy could be established. In these patients the mean (±SD) age was 27.3 (±6.7) years (ages ranged from 13 to 49 years). The race/ethnicity breakdown was 20% white, 25% African American, 40% Hispanic, and 14% Asian. Language spoken was English in 63%, Spanish in 30%, and Cantonese in 3%.

Of the 730 patients in the final study population, 96 (13%) had ectopic pregnancies (of which 49 were ruptured), 253 (35%) had abnormal intrauterine pregnancies, and 381 (52%) had normal intrauterine pregnancies. The pregnancy classifications were based on the initial ultrasound in 19% of the ectopic pregnancies, 23% of the abnormal intrauterine pregnancies, and 83% of the normal intrauterine pregnancies. The geometric mean β-hCG values were similar in the ectopic group (1,886 mIU/mL; 95% confidence interval [95% CI] = 1,305 to 2,725) and the abnormal intrauterine pregnancy group (2,022 mIU/mL; 95% CI = 1,588 to 2,576), while the geometric mean β-hCG value in the normal intrauterine pregnancy group was much higher (30,512 mIU/mL; 95% CI = 25,840 to 36,030). The differences between the means were statistically significant ($p < 0.0001$). However, on pairwise comparison, the difference between the means of the ectopic pregnancy and abnormal intrauterine pregnancy groups was not significant ($p = 0.95$). In the 66 patients who were lost to follow-up (i.e., the pregnancy type could not be determined based on the initial ED visit and no subsequent records were available), the geometric mean β-hCG was 1,462 mIU/mL (95% CI = 871 to 2,452). Figure 1 shows the β-hCG distributions of the three main pregnancy types on a modified log scale (see Methods). The β-hCG distributions of ectopic pregnancy and abnormal intrauterine pregnancy were similar, while the β-hCG distribution of normal intrauterine pregnancy was centered at substantially higher β-hCG levels.

The two ROC curves in Figure 2 present the frequency distributions in a different way; they show the sensitivity and false-positive rate (1 − specificity) at each potential β-hCG cutoff. One of the curves assumes that the β-hCG level is used to distinguish between ectopic and intrauterine pregnancies (normal and abnormal combined); the other assumes that the β-hCG level is used to differentiate between abnormal pregnancies (ectopic and abnormal intrauterine combined) versus normal intrauterine pregnancies. It is evident from these ROC curves, as well as from the frequency distributions in Figure 1, that the β-hCG level is much more useful for distinguishing abnormal from normal pregnancies than for distinguishing ectopic from intrauterine pregnancies. The slope of the ROC curve prior to each cutoff point is called the likelihood ratio and represents the percentage gain in sensitivity for each percentage point loss in specificity

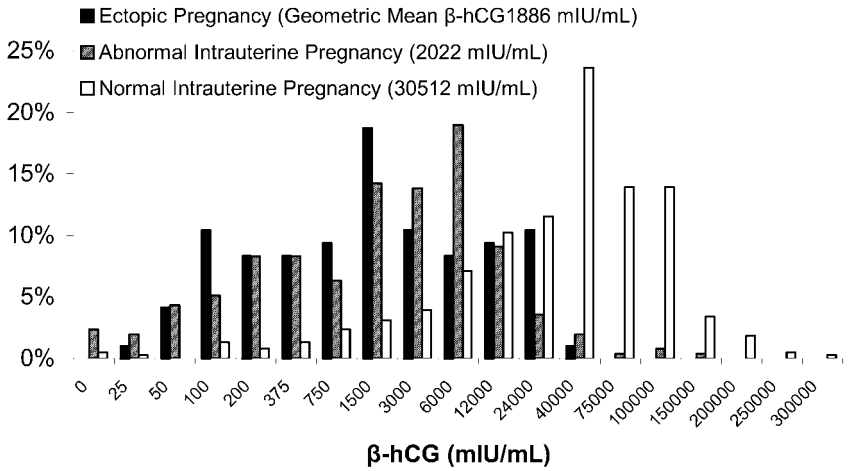

Figure 1. Beta-human chorionic gonadotropin (β-hCG) distributions (with geometric means) of patients with ectopic pregnancy, abnormal intrauterine pregnancy, and normal intrauterine pregnancy.

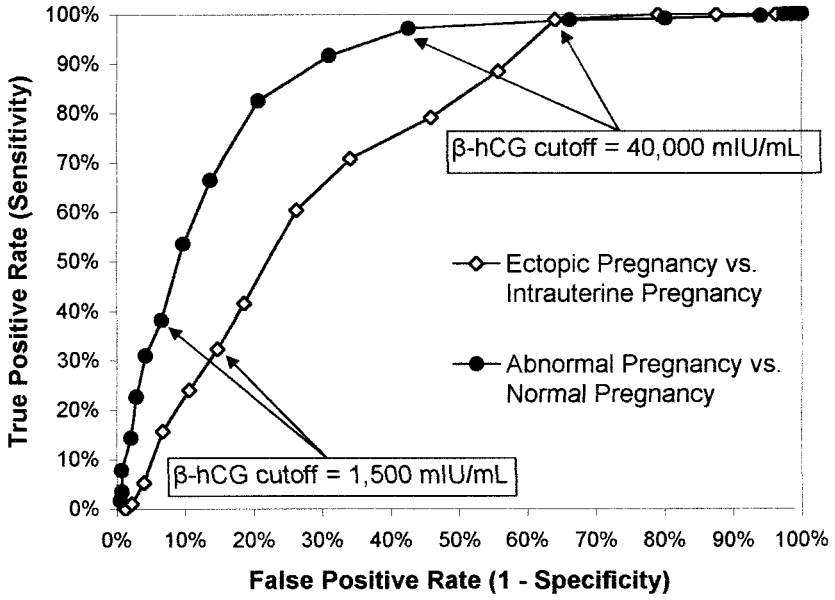

Figure 2. Receiver operating characteristic (ROC) curves showing true-positive rate (sensitivity) and false-positive rate (1 – specificity) for each of several potential beta-human chorionic gonadotropin (β-hCG) cut-points to separate a ''positive'' test (β-hCG < cutoff) from a ''negative'' test (β-hCG ≥ cutoff). In one curve, a below-cutoff value is considered positive for ectopic pregnancy; in the other curve, a below-cutoff value is considered positive for abnormal pregnancy (either intrauterine or ectopic). To identify ectopic pregnancy, a β-hCG cutoff of 1,500 mIU/mL had a sensitivity of 0.42 (95% CI = 0.32 to 0.52) and a specificity of 0.81 (95% CI = 0.78 to 0.84); a cutoff of 40,000 mIU/mL had a sensitivity of 0.99 (95% CI = 0.94 to 1.00) and a specificity of 0.36 (95% CI = 0.32 to 0.40).

associated with an increase (relaxation) of the cutoff to that level. A steep slope means raising the cutoff to that level results in a large gain in sensitivity for a small loss in specificity, while a gentle slope represents a small gain in sensitivity for a large loss in specificity. The optimal cutoff depends on these slopes (likelihood ratios), the pretest probability of disease, and the relative cost of a false negative versus a false positive. The existence of a single optimal cutoff requires a concave ROC curve (i.e., that the likelihood ratios decrease monotonically as the cutoff to identify ''positives'' is relaxed); this is not the case for the ROC curve using β-hCG to distinguish between ectopic and intrauterine pregnancies (Figure 2).

Table 2 shows how the different pregnancy types were distributed between three different β-hCG intervals: <1,500 mIU/mL, 1,500–49,999 mIU/mL, and ≥50,000 mIU/mL. These intervals were chosen for comparison with other studies.[6,12,26] Almost half (42%) of the ectopic pregnancies had β-hCG levels less than 1,500 mIU/mL; of the abnormal intrauterine pregnancies, 37% were below the threshold; while only 7% of the normal intrauterine pregnancies had β-hCG levels below the threshold. Overall, normal intrauterine pregnancy was much more common than ectopic pregnancy in this population of women presenting to the ED for abdominal pain or vaginal bleeding. However, those with β-hCG levels below the 1,500 mIU/mL threshold were substantially more likely to have ectopic pregnancies (n = 40) than to have normal intrauterine pregnancies (n = 25).

Comparing ectopic pregnancies with all intrauterine pregnancies, normal and abnormal combined, the likelihood ratio for ectopic pregnancy of a β-hCG less than 1,500 mIU/mL was 2.24 (Table 2). This means that a below-threshold β-hCG level more than doubled the pre-test odds of ectopic pregnancy. A below-threshold β-hCG level was even more useful at separating all abnormal pregnancies (ectopic and abnormal intrauterine) from normal intrauterine pregnancies. The likelihood ratio for abnormal vs. normal pregnancy of a β-hCG level less than 1,500 mIU/mL was 5.81 (Table 2). A β-hCG less than 40,000 mIU/mL had a sensitivity for ectopic pregnancy of 0.99 (95% CI = 0.94 to 1.00). (One of the 96 ectopic pregnancies—an unruptured tubal pregnancy—had an initial β-hCG of 66,200 mIU/mL.) The 40,000 mIU/mL cutoff also had a specificity of 0.36 (95% CI = 0.32 to 0.40), with most of the false positives being abnormal intrauterine pregnancies. A β-hCG greater than or equal to 40,000 mIU/mL decreased the odds of ectopic pregnancy by a factor of 33 (likelihood ratio = 0.03).

We present likelihood ratios, instead of prevalence (predictive values) within the β-hCG intervals, to allow use of our results in populations with different overall prevalence of ectopic pregnancy. In our population with an ectopic pregnancy prevalence of 13.2%, the predictive value of a β-hCG < 1,500 mIU/mL was 25.3% (CI = 18.7% to 32.8%). In other words, one fourth of the patients with below-threshold β-hCG levels had ectopic pregnancies. The proportion

TABLE 2. Likelihood Ratios for Three Beta-Human Chorionic Gonadotropin (β-hCG) Intervals to Distinguish Ectopic from Intrauterine Pregnancies or to Distinguish Normal from Abnormal Pregnancies

	Pregnancy Type*				Likelihood Ratio	
β-hCG (mIU/mL)	EP	AIU	NIU	IUP (AIU + NIU)	EP vs. IUP	EP + AIU vs. NIU
<1,500	40 (42%)	93 (37%)	25 (7%)	118 (19%)	2.24	5.81
≥1,500, <40,000	55 (57%)	151 (60%)	137 (36%)	288 (45%)	1.26	1.64
≥40,000†	1 (1%)	9 (4%)	219 (57%)	228 (36%)	0.03	0.05
Total	96	253	381	634		

*EP = ectopic pregnancy; AIU = abnormal intrauterine pregnancy; NIU = normal intrauterine pregnancy; IUP = intrauterine pregnancy.
†Sensitivity and specificity of β-hCG < 40,000 mIU/mL for EP were 0.99 (95% CI = 0.94 to 1.00) and 0.36 (95% CI = 0.32 to 0.40), respectively.

of patients in the below-threshold group with normal intrauterine pregnancies was 15.8% (CI = 10.5% to 22.4%).

DISCUSSION

This study of women presenting to an ED for abdominal pain or vaginal bleeding showed that abnormal pregnancies, whether intrauterine or ectopic, had similar β-hCG distributions, while normal pregnancies had much higher β-hCG levels. Even though most pregnant women presenting to the ED with abdominal pain or vaginal bleeding had normal intrauterine pregnancies, those with β-hCG levels less than 1,500 mIU/mL were unlikely to have normal pregnancies.

In a similar but smaller population of 309 symptomatic patients who had both β-hCG levels and final diagnoses determined, Barnhart et al.[6] found a lower prevalence of ectopic pregnancy (n = 27, 8.7%) but similar β-hCG distributions. The proportions of patients with ectopic, abnormal intrauterine, and normal intrauterine pregnancies who had β-hCG less than 1,500 mIU/mL were 44%, 48%, and 6%, respectively. (Our results were: ectopic 42%, abnormal intrauterine 37%, and normal intrauterine 7%.) For Barnhart et al., the likelihood ratio for ectopic versus intrauterine pregnancy (abnormal or normal) of a β-hCG level less than 1,500 mIU/mL was 2.46 (our result was 2.24). The Barnhart results mean that a β-hCG level less than 1,500 mIU/mL increases the odds of ectopic pregnancy by two and a half.

In general, when one is using a continuous measurement, such as β-hCG, to determine the presence or absence of a disease, such as ectopic pregnancy, one chooses a cutoff value for the measurement that determines whether the test is ''positive'' or ''negative'' for the disease. Any result on the side of the cutoff where disease is more likely (i.e., with the higher likelihood ratio) is considered ''positive.'' The optimal cutoff is determined by the pre-test probability of disease, the relative cost of misclassifying an individual with the disease as negative (a false negative) versus the cost of misclassifying an individual without the disease as positive (a false positive), and the measurement's frequency distribution in diseased and non-diseased individuals (or the resulting likelihood ratios). If one views the β-hCG in this way and accepts the cutoff of 1,500 mIU/mL, it is clear that results less than 1,500 mIU/mL should be considered ''positive'' for ectopic pregnancy.

Several older protocols for diagnosing ectopic pregnancy in ED patients with abdominal pain or vaginal bleeding deferred ultrasound in women with β-hCG levels below 1,500 mIU/mL.[6,12] The reason for this was the poor sensitivity of ultrasound for normal intrauterine pregnancies with low β-hCG levels. However, since transvaginal ultrasound can also identify findings consistent with ectopic pregnancy or abnormal intrauterine pregnancy, and since (as confirmed here) the risk of ectopic pregnancy is substantially higher in women with below-threshold β-hCG levels, most authors (including those who once advocated deferring ultrasound[15]) now agree that transvaginal ultrasound is indicated in all women at risk for ectopic pregnancies.[1,16,27] The β-hCG level is mainly helpful to stratify risk in women whose initial ultrasound is indeterminate—diagnostic of neither intrauterine pregnancy nor ectopic pregnancy.[28] Nevertheless, at some hospitals, protocols persist that defer ultrasound for below-threshold β-hCG levels, and at other hospitals, endovaginal ultrasound may not be routinely available. In these hospitals, emergency physicians must still use the single β-hCG level to stratify risk for ectopic pregnancy without the benefit of a transvaginal ultrasound result.

Marill et al.[26] compared the β-hCG levels of women (mainly ED patients) who had ectopic pregnancy with the levels of women who received an ED diagnosis of threatened abortion but ultimately delivered a baby (same gestation) at their hospital. The main question was whether there was a β-hCG level above which ectopic pregnancy was so unlikely that ultrasound could be avoided. The omission of patients with abnormal intrauterine pregnancies diminishes the usefulness of the study results to the clinician evaluating ED patients with pain or bleeding, since more than one third of these patients have abnormal

intrauterine pregnancies. Also, Marill et al. reported ROC curves but not the corresponding frequency distributions or likelihood ratios. Their overall conclusion was that a low β-hCG level increases the likelihood of ectopic pregnancy, but women with high β-hCG levels (>40,000 mIU/mL) still require ultrasound, because two of their 212 patients with ectopic pregnancies had β-hCG levels > 40,000 mIU/mL. Similarly, one of our 96 patients with ectopic pregnancy had β-hCG level > 40,000 mIU/mL.

Mol et al.[16] encourage the use of "probabilistic decision rule" to diagnose ectopic pregnancy. This means estimating the pretest probability of ectopic and using the likelihood ratios associated with particular test results to update this probability. Their likelihood ratios assume that the transvaginal ultrasound is done first and that the β-hCG result is used only to update probability in those patients with nondiagnostic ultrasounds. Our likelihood results will be useful to those clinicians who do not have the benefit of the transvaginal ultrasound result and must update the probability of ectopic pregnancy based on the β-hCG level alone. We show that a β-hCG level of 40,000 mIU/mL or greater is extremely comforting, although it does not completely exclude the possibility of ectopic pregnancy. More importantly, we show that a β-hCG level less than 1,500 mIU/mL is predictive for ectopic pregnancy and substantially reduces the likelihood of normal pregnancy, although normal pregnancy is not excluded.

LIMITATIONS

Our rate of ectopic pregnancy (13%) was at the high end of the range of 8% to 13% reported in similar studies.[3,6,29–31] Since we report likelihood ratios in addition to prevalences, we hope that our results will be useful in settings with different rates of ectopic pregnancy. The rate of ectopic rupture in this study was quite high at 49 out of 96 (51%). Buckley et al.[30] and Mol et al.[32] had rupture rates of 12 in 39 (31%) and 65 in 288 (23%), respectively. However, their populations were very different from ours. Our population undoubtedly has a higher rate of rupture, but this difference also may mean that our threshold for classifying an ectopic pregnancy as ruptured was lower than in the other studies. For example, if on laparoscopy the patient was noted to have bled significantly through the fimbriated end of the fallopian tube, we classified the ectopic pregnancy as ruptured. We did not compare the β-hCG levels in the ruptured and unruptured subgroups, but we plan to do so in a subsequent study.

The chart abstractors in this study may have seen the patient's β-hCG level prior to classifying the pregnancy type. However, we used explicit outcome classification criteria and do not believe that this possible foreknowledge of the predictor affected or biased outcome classification. With regard to patients lost to follow-up, most normal intrauterine pregnancies were classified on the basis of the ED record at the index visit. Therefore, the 66 patients whose outcomes could not be classified on the basis of the ED record and who did not have subsequent follow-up were more likely to have had abnormal pregnancies (intrauterine or ectopic). Consistent with this, the mean β-hCG in this group was very low.

CONCLUSIONS

In women with abdominal pain or vaginal bleeding and serum β-hCG levels less than 1,500 mIU/mL, the risk of ectopic pregnancy is substantially increased, while the likelihood of normal intrauterine pregnancy is low. The β-hCG level is more useful in distinguishing abnormal from normal pregnancies than it is for distinguishing ectopic from intrauterine pregnancies.

References

1. Tay JI, Moore J, Walker JJ. Ectopic pregnancy. BMJ. 2000; 320:916–9.
2. Ankum WM. Diagnosing suspected ectopic pregnancy. Hcg monitoring and transvaginal ultrasound lead the way. BMJ. 2000; 321:1235–6.
3. Kaplan BC, Dart RG, Moskos M, et al. Ectopic pregnancy: prospective study with improved diagnostic accuracy. Ann Emerg Med. 1996; 28:10–7.
4. Mehta TS, Levine D, Beckwith B. Treatment of ectopic pregnancy: is a human chorionic gonadotropin level of 2,000 mIU/mL a reasonable threshold? Radiology. 1997; 205:569–73.
5. Counselman FL, Shaar GS, Heller RA, King DK. Quantitative β-hCG levels less than 1000 mIU/mL in patients with ectopic pregnancy: pelvic ultrasound still useful. J Emerg Med. 1998; 16:699–703.
6. Barnhart KT, Simhan H, Kamelle SA. Diagnostic accuracy of ultrasound above and below the beta-hCG discriminatory zone. Obstet Gynecol. 1999; 94:583–7.
7. Kohn MA. Diagnostic accuracy of ultrasound above and below the beta-hCG discriminatory zone [letter; comment]. Obstet Gynecol. 2000; 95:475–6.
8. Nyberg DA, Mack LA, Harvey D, Wang K. Value of the yolk sac in evaluating early pregnancies. J Ultrasound Med. 1988; 7:129–35.
9. Bree RL, Edwards M, Bohm-Velez M, Beyler S, Roberts J, Mendelson EB. Transvaginal sonography in the evaluation of normal early pregnancy: correlation with HCG level [see comments]. Am J Roentgenol. 1989; 153(1):75–9.
10. ACOG. ACOG Technical Bulletin. Gynecologic ultrasonography. Number 215, November 1995. Int J Gynaecol Obstet. 1996; 52:293–304.
11. Barnhart KT, Mennuti MT, Benjamin I, Jacobson S, Goodman D, Coutifaris C. Prompt diagnosis of ectopic pregnancy in an emergency department setting. Obstet Gynecol. 1994; 84:1010–5.
12. Braffman BH, Coleman BG, Ramchandani P, et al. Emergency department screening for ectopic pregnancy: a prospective US study. Radiology. 1994; 190:797–802.
13. Ankum WM, Van der Veen F, Hamerlynck JV, Lammes FB. Transvaginal sonography and human chorionic gonadotropin measurements in suspected ectopic pregnancy: a detailed analysis of a diagnostic approach. Hum Reprod. 1993; 8:1307–11.
14. Dart RG, Mitterando J, Dart LM. Rate of change of serial beta-human chorionic gonadotropin values as a predictor of ectopic

pregnancy in patients with indeterminate transvaginal ultrasound findings. Ann Emerg Med. 1999; 34:703–10.
15. Gracia CR, Barnhart KT. Diagnosing ectopic pregnancy: decision analysis comparing six strategies. Obstet Gynecol. 2001; 97:464–70.
16. Mol BW, van Der Veen F, Bossuyt PM. Implementation of probabilistic decision rules improves the predictive values of algorithms in the diagnostic management of ectopic pregnancy. Hum Reprod. 1999; 14:2855–62.
17. Dart RG, Burke G, Dart L. Subclassification of indeterminate pelvic ultrasonography: prospective evaluation of the risk of ectopic pregnancy. Ann Emerg Med. 2002; 39:382–8.
18. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: where are the methods? Ann Emerg Med. 1996; 27:305–8.
19. Kadar N, Caldwell BV, Romero R. A method of screening for ectopic pregnancy and its indications. Obstet Gynecol. 1981; 58:162–6.
20. Romero R, Kadar N, Copel JA, Jeanty P, DeCherney AH, Hobbins JC. The value of serial human chorionic gonadotropin testing as a diagnostic tool in ectopic pregnancy. Am J Obstet Gynecol. 1986; 155:392–4.
21. Braunstein GD, Karow WG, Gentry WC, Rasor J, Wade ME. First-trimester chorionic gonadotropin measurements as an aid in the diagnosis of early pregnancy disorders. Am J Obstet Gynecol. 1978; 131:25–32.
22. Braunstein GD, Rasor J, Danzer H, Adler D, Wade ME. Serum human chorionic gonadotropin levels throughout normal pregnancy. Am J Obstet Gynecol. 1976; 126:678–81.
23. Pittaway DE, Reish RL, Wentz AC. Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies. Am J Obstet Gynecol. 1985; 152:299–302.
24. Shepherd RW, Patton PE, Novy MJ, Burry KA. Serial beta-hCG measurements in the early detection of ectopic pregnancy [see comments]. Obstet Gynecol. 1990; 75(3 pt 1):417–20.
25. Dart R, Dart L, Mitchell P. Normal intrauterine pregnancy is unlikely in patients who have echogenic material identified within the endometrial cavity at transvaginal ultrasonography. Acad Emerg Med. 1999; 6:116–20.
26. Marill KA, Ingmire TE, Nelson BK. Utility of a single beta HCG measurement to evaluate for absence of ectopic pregnancy. J Emerg Med. 1999; 17:419–26.
27. Dart RG. Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med. 1999; 33:310–20.
28. Mol BW, Hajenius PJ, Engelsbel S, et al. Serum human chorionic gonadotropin measurement in the diagnosis of ectopic pregnancy when transvaginal sonography is inconclusive. Fertil Steril. 1998; 70:972–81.
29. Mateer JR, Aiman EJ, Brown MH, Olson DW. Ultrasonographic examination by emergency physicians of patients at risk for ectopic pregnancy. Acad Emerg Med. 1995; 2:867–73.
30. Buckley RG, King KJ, Disney JD, Ambroz PK, Gorman JD, Klausen JH. Derivation of a clinical prediction model for the emergency department diagnosis of ectopic pregnancy. Acad Emerg Med. 1998; 5:951–60.
31. Durham B, Lane B, Burbridge L, Balasubramaniam S. Pelvic ultrasound performed by emergency physicians for the detection of ectopic pregnancy in complicated first-trimester pregnancies. Ann Emerg Med. 1997; 29:338–47.
32. Mol BW, Hajenius PJ, Engelsbel S, et al. Can noninvasive diagnostic tools predict tubal rupture or active bleeding in patients with tubal pregnancy? Fertil Steril. 1999; 71: 167–73.