Following declining human chorionic gonadotropin values in pregnancies of unknown location: when is it safe to stop?

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Objective: To determine if the pattern of decline in hCG curves can discriminate spontaneous abortion (SAB) from ectopic pregnancy (EP).
Design: Retrospective cohort study.
Setting: University hospitals.
Patient(s): A total of 1,551 women with symptomatic pregnancy of unknown location (PUL) and decreasing hCG values.
Intervention(S): None.
Main Outcome Measure(s): Percentage change in hCG; days and visits to final diagnosis.
Result(s): Of the 1,551 women with a PUL and declining hCG, 146 were ultimately diagnosed with EP and 1,405 with SAB. An 85% hCG drop within 4 days or a 95% hCG drop within 7 days both ruled out an EP 100% of the time. Applying the 4-day cutoff to this population would have saved 16% of the SAB population (229/1,405) a total of 2,841 person-days and 277 clinical visits. Applying the 7-day cutoff would have saved 9% of the SAB population (126/1,405) a total of 1,294 person-days and 182 clinical visits. These cutoffs were separately validated on a group of 179 EPs collected from three university clinical centers. In that population, each cutoff separately ruled out EP 100% of the time.
Conclusion(s): The decline in serum hCG is slower in EPs than in SAB and can be used to aid clinicians in the frequency and duration of follow-up. Costs and patient time may be saved by allowing women who meet one of these criteria to be followed less frequently. (Fertil Steril® 2016;105:953–7. ©2016 by American Society for Reproductive Medicine.)
Key Words: hCG curves, ectopic pregnancy, pregnancy of unknown location

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Ectopic pregnancy (EP) has been reported to range from 0.64% to 2.62% of all pregnancies in the United States (1, 2) and accounts for 0.5 maternal deaths per 100,000 live births (3). Clinical history, serum quantitative hCG measurement, and transvaginal sonography (TVS) are the basic tools for the evaluation of symptomatic early pregnancies (4–6); however, definitive diagnosis may be challenging in some cases (4, 5). Twenty-five percent to 50% of women with EP initially receive the diagnosis of pregnancy of unknown location (PUL) (7, 8), a term used when no evidence of either EP or intrauterine pregnancy (IUP) on TVS is recognized (9). The work-up for PUL includes serial serum hCG tests, TVS, and, occasionally, dilation and curettage (4, 10). This algorithm can be time

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consuming and costly for the health care system and the patient (11).

During the past decade, the hCG curves for a viable IUP and a miscarriage have been defined and refined by our group (12–14). In contrast, there is no single pattern of hCG able to characterize EP (15, 16). In fact, there is significant overlap between the curves of EPs, spontaneous abortions (SABs), and viable IUPs (16). In women with PULs with decreasing hCG measurements, serial hCG measurements that decline more slowly than established thresholds (21%–35% 2 days after presentation and 60%–84% at 7 days) are considered to be at risk for EP (14). However, one study has demonstrated that among EPs with decreasing hCG curves, up to 23% of the curves can "mimic" or decline at a rate of, an intrauterine SAB (16), which makes this a challenging diagnostic dilemma.

With the present study, we aimed to examine the hCG profiles of women with EP and SAB with decreasing hCG values to determine if there is a threshold at which the risk of an EP is effectively eliminated, and to assess the impact of the application of such criteria on patient and clinical encounter time.

MATERIALS AND METHODS

This study was conducted primarily at one site, the University of Pennsylvania, as part of the Predictors of Ectopic Pregnancy Study. Data for the analysis were collected over a 17-year period from 1990 to 2007 at the University of Pennsylvania with the use of a centralized computerized database of women who presented in the 1st trimester of pregnancy with pelvic pain and/or vaginal bleeding.

Subjects were included if they: 1) presented with a PUL as defined by internationally accepted nomenclature (9); 2) had at least two hCG values 1–7 days apart; and 3) had an overall declining hCG trend, as defined by a final hCG value less than the presentation value. At the time of identification of a PUL, patients were instructed to report for follow-up hCG measurements every 2 days. All patients included in this analysis had a documented date of eventual definitive diagnosis of SAB or EP. Patients were excluded if they had multifetal gestations, heterotopic pregnancy, or concern for gestational trophoblastic disease.

Diagnosis of EP was confirmed by evidence of products of conception in the fallopian tube or when endometrial curettage failed to reveal products of conception. Diagnosis of SAB was defined as a spontaneous decline of hCG levels to <5 mIU/mL in the absence of surgical or medical intervention, or as the presence of products of conception on dilation and curettage. The analysis was restricted to hCG values before and including the date of diagnosis. The data from women with SABs who had dilation and curettage procedures were censored at the time of surgery to focus on the portion of the curve that represented spontaneous decline.

Clinical characteristics for women with EP and SAB were compared with the use of descriptive statistics including Student *t* tests or the chi-square test where appropriate. Characteristics of the hCG trend were also compared between the two groups. Days to diagnosis, total hCG percentage drop, and percentage drops from initial hCG at 4 days, 1 week, and 2 weeks were compared with the use of 90th, 95th, and 99th percentile distributions. Percentage drop was calculated for discrete time points with the use of both a "within *x* days" and an interpolated model when day 4, 7, or 14 hCG values were not available. For example, if a participant had hCG values measured on day 1, day 3, day 6, and day 9, the "within 4 days" decline was calculated as the percentage decline from day 1 to day 3, whereas the interpolated decline was calculated as the percentage decline from day 1 to the predicted hCG value on day 4, using the day 3 and day 6 values for linear interpolation. The distributions of percentage drop at each specific day were described for EPs and SABs with the use of summary statistics. Groups were compared with the use of Wilcoxon rank sum tests.

Clinical cutoffs below which EPs were excluded were established. These cutoffs were then used to calculate the number of health care encounters and the number of person-days that would have been saved in the SAB group had these cutoffs been applied and no further follow-up obtained. Number of clinic visits was calculated by tabulating the number of subsequent hCG values collected between the cutoff and when the hCG was <5 mIU/mL. Person-days was calculated by tabulating the number of days elapsed from when the clinical cutoff was achieved to when the hCG was <5 mIU/mL in SAB participants.

After clinical cutoffs were established for excluding an EP, these cutoffs were validated in a new cohort of women from three racially and ethnically diverse academic centers using the same inclusion criteria as the primary cohort. The validation cohort comprised clinical data collected from at three sites, the University of Pennsylvania, the University of Miami, and the University of Southern California, also as part of the Predictors of Ectopic Pregnancy Study. Institutional Review Board approval was obtained at each site. The patients included in this validation cohort were enrolled from August 2007 to June 2009, and data were collected in a manner identical to the primary cohort. Clinical characteristics of the women with EP in the derivation cohort were compared with the validation cohort by means of descriptive summary statistics. The criteria for ruling out an EP established from the derivation cohort were applied to the validation cohort.

Because this was a pragmatic trial using standard clinical care, serum hCG concentration measures were performed at the clinical laboratory of each participating center. All clinical laboratories were College of American Pathologists certified.

RESULTS

Data were collected for a total of 3,563 PULs during the study period (Fig. 1). Of these, there were 1,551 PULs with declining hCG values included in the derivation cohort. Compared with those lost to follow-up, the participants included in this analysis were of similar age ($P=.74$) and gravidity ($P=.34$).

Of the 1,551 pregnancies included in this analysis, 1,405 participants were ultimately diagnosed with SAB and 146 with EP. The mean age of the population was 25.4 years with average gravidity and parity of 2.4 and 0.91, respectively. A total of 79% of the cohort were African American. Descriptive characteristics of participants with SABs compared with participants with EPs are presented in