ORIGINAL ARTICLE: EARLY PREGNANCY

Temporal refinement does not affect predicted human chorionic gonadotropin rise in early pregnancy

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Objective: To examine the impact of validation and temporal resolution of estimation of hCG increase, because patients' hCG values are not obtained at precise daily increments or always in the same laboratory.
Design: Retrospective cohort study of women presenting with nondiagnosed symptomatic first-trimester pregnancies who had serial hCG level measurements over time.
Setting: Not applicable.
Patient(s): A total of 171 women presenting from September 2007 to February 2010 with first-trimester pregnancy pain and/or bleeding for whom a normal intrauterine pregnancy was ultimately confirmed.
Interventions: None.
Main Outcome Measure(s): Serial hCG values, time period between hCG measurements, hCG rise.
Result(s): After data verification, 118 subjects contributing 327 values met inclusion criteria and passed data verification for analysis with improved temporal precision. The more precise data showed a steeper hCG rise, and the predicted 2-day hCG increase at the 1st percentile was slightly faster (1.68-fold vs. 1.56-fold) than the "raw" clinical data and previous models.
Conclusion(s): Data verification and improved temporal precision suggested a faster hCG increase in early intrauterine gestation than previously demonstrated. Because laboratory variation and temporal imprecision are common, these data demonstrate that current modeling of the expected rise of hCG in a normal gestation is valid and appropriately conservative in the determination of a nonviable gestation. No change in the minimal threshold for potential viability is recommended. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Early gestation viability, human chorionic gonadotropin, hourly precision

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Serial measurements of serum hCG are routinely used to evaluate the viability of a symptomatic early pregnancy, thereby guiding practitioners on the proper course of management. Of essential importance is characterizing the natural trend of the hCG rise in the first trimester. Several studies have characterized the rise of hCG in both normal and abnormal pregnancies before the gestational age at which ultrasound may be used for definitive diagnosis of a viable intrauterine pregnancy (1–7). These studies established a threshold "minimal rise" above which pregnancies can be expectantly managed and below which pregnancies may be deemed to be "abnormal" and either surgically or medically treated. The slowest, minimal rise for a normal viable intrauterine pregnancy was a 53% rise over 2 days (using a 1st percentile cutoff) (4, 5). However, other studies have shown that using a minimal rise as low as 35% in 2 days may lead to the misclassification of a number of normal pregnancies as nonviable (8). For these studies, the precise timing of the serum hCG collection was not known, and for modeling purposes the

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time between serial assessments was rounded to daily (24-hour) increments.

Given the clinical importance of accurate calculation of the relative rise in serum hCG, we aimed to establish that the current method of quantifying follow-up time was valid and did not introduce systematic bias. The present study examined the impact of using more precise follow-up times (hours rather than days) on the characterization of normal serial hCG curves in patients displaying pelvic or abdominal pain and/or vaginal bleeding with early viable gestations. The purpose of this study was to provide insight as to whether clinical management needs to be amended if patients do not get hCG values precisely 48 hours apart or if hCG values are evaluated at different laboratories.

MATERIALS AND METHODS

In this study we generated a model of hCG increase using similar techniques to our initial publication (4), but in a new population sample. We assessed how the model differed when the data in the clinical database were validated with medical records, with and without inclusion of values from outside laboratories, and when the time period between hCG measurements used actual hours rather than measurement times rounded to whole days. This study was approved by the Institutional Review Board of the University of Pennsylvania, and every study patient gave informed consent.

The Hospital of the University of Pennsylvania maintains a clinical database which tracks all patients presenting to the emergency department with a symptomatic first-trimester pregnancy, at risk for miscarriage or ectopic pregnancy, who are not diagnosed at their initial visit. Data were extracted from this database for women who presented from September 2007 to February 2010 with pelvic or abdominal pain and/or vaginal bleeding. A nondiagnostic initial evaluation was defined by a history of a positive serum hCG and an ultrasound with no evidence of an intrauterine or extrauterine gestational sac (9).

Women were included in the review if they had at least two hCG values from 1 to 7 days apart with the first value being >5 mIU/mL, a known final definitive diagnosis of intrauterine pregnancy (including a gestational sac with either a yolk sac or a fetal pole documented by means of ultrasound), and all of their care was received at the University of Pennsylvania. hCG values were included only if they had a corresponding date of laboratory draw and were ≤10,000 mIU/mL. Serum hCG concentrations were determined with the use of the Abbot Axsym total beta immunoassay (Abbot Laboratories), and results are expressed as mIU/mL, using the Third International Reference Preparation. Serial hCG values were excluded from review if the date of draw occurred after the date of definitive diagnosis. Women whose hCG values recorded in the clinical database met the inclusion/exclusion criteria were identified by means of birth date and medical record number. The full list of laboratory values for each patient was queried in the electronic medical record (EMR) system (Medview; Healthslide) of the University of Pennsylvania, which contains laboratory data for each of its three hospitals. Serum hCG values as recorded in the clinical database were searched for and identified in the EMR. After assessment of accuracy of the value as recorded in the computerized database, the time of the hCG serum collection as reported in the EMR was recorded.

For each woman, an hCG profile was constructed for hCG values drawn between the date of initial presentation and the date of definitive diagnosis as reported in the clinical database and the EMR. For all analyses, time was measured as days from the date of initial hCG value to the date and time of a given laboratory draw as reported in the clinical database or EMR. For modeling, hCG values were transformed to a natural log scale, ln(hCG), to better approximate a normal distribution while reducing the influence of large values. Longitudinal analyses were conducted using linear random effects techniques. These methods estimate a population average curve by aggregating estimated hCG profiles from each individual subject. Application of these models accounts for the correlation in repeated measurements of hCG contributed by each subject and allows for variation in the number and timing of observations (10). Both linear and quadratic effects for time were considered as well as random linear and quadratic slopes. Model fit was assessed by means of Akaike information criteria (11). The most parsimonious model included a fixed effect for linear time and a random intercept.

An essential component of the internal validation process was to assess the accuracy of the data reported in the clinical database used to model the hCG curves. Internal validation was achieved by comparing both the date of draw and the hCG quantity. If a discrepancy in either the date of draw or the hCG quantity existed between the clinical database and the EMR, the study data record was adjusted to reflect the EMR data and the data value was annotated in the record as such. Data values that appeared in the EMR and occurred between the date of initial visit and the date of definitive diagnosis but were not originally entered into the clinical database by the practitioner were annotated and included in the analysis. Furthermore, hCG values for patient records that could not be found in the EMR could not be validated and therefore were annotated and analyzed separately.

Population average estimates of slope, standard errors, and upper and lower 95% confidence bounds for the rate of increase in ln(hCG) were estimated from a multivariate linear regression model that assumed a normal distribution for ln(hCG). Primary data management and analyses, including regression modeling, were conducted with the use of Stata version 11.2 (Statacorp). The relative rise in serum hCG concentration for a 1-day change in hCG was calculated as the exp{slope}, a 2-day relative rise as exp{2*slope}. Confidence bounds for the relative rise were derived by exponentiation of corresponding bounds for the slope. We present 1-day, 2-day, 4-day, and 7-day slope and relative rise along with 1st, 5th, 10th, and 50th percentile estimates of viable intrauterine pregnancies. The relative rises, along with 95% confidence intervals, were estimated by means of a boot strap resampling of the original cohort size 1,000 times.

To characterize the independent impact of improved temporal precision, slopes and predicted rise were compared between validated data analyzed with day-precision to validated data analyzed with hour-precision, and histograms