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Predicting the Decline in Human Chorionic Gonadotropin in a Resolving Pregnancy of Unknown Location

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Abstract

Objective—To characterize the curve derived from serial human chorionic gonadotropin (hCG) values in women with spontaneous resolution of pregnancy of unknown location and to assess factors that modify the decline.

Methods—Data from three sites were extracted from a clinical database of women with a symptomatic pregnancy of unknown location that required follow-up with serial hCG levels. A nonlinear, mixed-effects, regression model was used to generate hCG elimination curves.

Results—Four hundred forty-three women presenting with a pregnancy of unknown location which resolved without intervention were studied between September 2007 and May 2009. Women older than 35 years had a slower hCG decline ($P=.001$) and those with pain had a steeper decline ($P=.006$), but these changes did not alter the curve in a clinically meaningful way. The decline in hCG is faster for those with a higher level at presentation. The average decline of hCG in women with spontaneous resolution is slower than previously reported. However, the minimal decline in hCG for women with spontaneous resolution of a pregnancy of unknown location ranged from 35% to 50% at 2 days of follow-up and 66% to 87% at 7 days, more rapid than previously reported.

Conclusion—In a diverse population, using updated statistical methods, it was observed that the minimal decline in hCG for women with spontaneous resolution is more rapid than previously reported. A decline slower than these thresholds may indicate the presence of retained trophoblastic tissue or ectopic pregnancy.

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INTRODUCTION

Miscarriage is the most common complication of early pregnancy and is a particular concern when bleeding is a presenting symptom (1–4). A combination of serial human chorionic gonadotropin (hCG) measurements and ultrasonography has been demonstrated to be the optimal strategy to determine embryonic viability and to ensure that appropriate interventions are performed, especially if there is a concern for ectopic pregnancy (5). The accurate diagnosis of miscarriage is complicated in symptomatic women who present with an ultrasonogram that is initially nondiagnostic (6, 7). Serial hCG measurements that are below the minimal rise (less than 53% over 48 hours) (8) may be predictive of a nonviable pregnancy, but provide limited discrimination between a miscarriage (9) and an ectopic pregnancy (10). Our previous research defined the natural decline in hCG in an urban-dwelling population of women who presented for evaluation of pain and bleeding with an unconfirmed diagnosis at presentation and an ultimate diagnosis of miscarriage (11). In this population, a quadratic curve for log hCG was determined to best fit the pattern of hCG decline. The minimal rate of decline in patients with miscarriage was found to be more rapid for women who presented with higher initial hCG concentrations, and ranged from 21% to 35% 2 days after presentation or 60% to 84% at 7 days of follow-up (12). A woman with a decline in hCG slower than this threshold was considered at risk for an ectopic pregnancy.

The primary aim of this research was to redefine the natural decline of hCG in women presenting with a pregnancy of unknown location and ultimately diagnosed with a resolved pregnancy of unknown location. An updated nonlinear mixed effects model was utilized to derive curves representing hCG elimination in a geographically and racially diverse national cohort. In addition, demographic variables and risk factors for miscarriage were evaluated for their potential effect on the longitudinal profiles of serial hCG measurements in women with miscarriage.

MATERIALS AND METHODS

Clinical data used for this study was collected at three sites: The University of Pennsylvania, The University of Miami, and The University of Southern California as part of the Predictors of Ectopic Pregnancy Study. Institutional Review Board approval was obtained at each site. Data were collected from September 2007 through May 2009. The cohort for this study consisted of women who presented with pain, bleeding, or both and a positive pregnancy test. Clinical data from each site were entered into a centralized database that was queried for this investigation. The study was powered to be able to estimate a sensitivity of 80% for the prediction of ectopic pregnancy compared with nonectopic (miscarriage and viable intrauterine gestation) with a 95% confidence interval of $\pm 5\%$. These calculations also assumed that the outcomes would be distributed as 18.6% ectopic pregnancy, 26% viable intrauterine pregnancy, and 55.4% miscarriage.

To be eligible for study, each woman had to have a nondiagnostic transvaginal ultrasonogram at presentation (no evidence of an intrauterine or extrauterine gestational sac), an initial hCG value of less than or equal to 10,000 milli-international units/mL, and follow-up with serial hCG measurements to determine the definitive diagnosis. The diagnosis of resolved pregnancy of unknown location was defined as a spontaneous fall of hCG to less than 5 milli-international units/mL (the lower limit of detection for the hCG assay used) or at least three declining hCG values with the final hCG less than 25 milli-international units/mL. Of note, the data were also censored at hCG values of 10 milli-international units/mL or less at which point values were treated effectively as undetectable. Only women with declining hCG levels without medical or surgical intervention were

enrolled in the study. All information up to 35 days from presentation was included in the analysis and used for creation of the final model.

Serum hCG concentrations were quantified using a chemiluminescent technique (AxSYM; Abbott Laboratories, Abbott Park, Illinois) and reported in milli-international units/mL using the Third International Reference Preparation (coefficient of variation 7.8). Information concerning last menstrual period, race, ethnicity, and maternal age were collected at the time of initial visit.

Analyses were conducted using the natural log transformation of the hCG values to reduce the skewness of the distribution and reduce the influence of large values. In order to reproduce our original paper (11), a linear random effects model was utilized to estimate the hCG slope per participant along with predictive intervals, or upper and lower confidence bounds (percentiles) for those slopes. In addition, we used a nonlinear mixed effects model which included random effect on the time axis to estimate the average shift at each site and allowed an additional shift by each person relative to the average. This approach, known as curve registration (12) allows the curve to be shifted for each respondent by an amount of days from the presentation date to align the rate and generate the best fitting overall curves. With the use of this second model, there was no need to know the date of the last menstrual period. The model computed a revised days-from-presentation variable (called “tau” in this paper to distinguish it from “time”) using a shift in days for each respondent that was composed of a specific fixed effect for their site plus a random effect due to each individual. This new day variable “lined up” the respondents based on their values and the shape of their individual curve. “Tau” was defined as:

Tau=days from presentation+*a* shift for site+*a* per participant shift (ie, random effect).

Using this shift, we tested both a linear model and a quadratic model for tau:

$$\begin{aligned}\text{Linear model: } \log_{-} \text{hCG} &= \text{intercept} + b_1 \times \text{tau.} \\ \text{Quadratic model: } \log_{-} \text{hCG} &= \text{intercept} + b_1 \times \text{tau} + b_2 \times \text{tau}^2.\end{aligned}$$

Versions of these models were compared to determine whether the time shift could account for the effects of sites and whether a linear model would be adequate over a short range of time from presentation. In addition, covariates including race, the presence of bleeding, and other demographic and clinical variables were explored to determine whether different predictive models would be needed for patients with these covariates.

To create tables of predicted hCG values, we first ran the models taking out the fixed effects for the sites. The rationale for this was that when we apply that to the prediction of hCG values for a new site, the effect of that site would be unknown. Doing so slightly increased the variance of the prediction, resulting in slightly wider prediction interval ranges (ie, bounds). We then computed a starting value of tau based on the initial hCG value. Higher hCG values shift a person closer to the presentation date, thus moving them into an area of the curve with a steeper or more rapid decline. Second, we computed the expected change in hCG values across time periods of 1, 2, 3, 4, and 7 days. Third, we computed the “percentile ranges” in these values using estimated standard errors for the slope parameters and percentiles of the per-person shift variable tau. Thus, the fall listed for percentile 95 means that only 5% of the patients with a resolved pregnancy of unknown location would have a decline in hCG this slow or slower.

To determine the best method for combining the data from the three sites, we created a model with the three sites as parameters. In a second model, we added a time shift for each site. When we added the time shift, the significance level for the three sites was reduced to nonsignificance. To determine whether a linear model for these data would be adequate over a restricted range instead of a quadratic model, we compared the fit of the linear, quadratic and cubic models using the likelihood ratio test. The quadratic model fit the data better and was used to generate the estimates. The scale of the graph is in the “new days” variable, labeled “tau;” thus, the time scale is not in days from presentation at the clinic, but rather shifted days.

Predicted hCG curves derived from this method determined the minimum expected hCG decline in a resolved pregnancy of unknown location. From a clinical perspective, once the observed rate of decline in hCG becomes less than the minimum defined by the curve, the patient is classified as having a suspected ectopic pregnancy. Two such scenarios for different initial hCG concentrations are represented graphically in Figures 1A and 1B.

All analyses were conducted in SAS version 9.2, Proc Mixed and Nlmixed.

RESULTS

The initial sample included 518 women who presented with a pregnancy of unknown location and were diagnosed with a spontaneously resolved pregnancy of unknown location. A total of 33 women were excluded that did not have at least two hCG values separated less than 7 days, and 42 were excluded because the initial hCG values were above 10,000 milli-international units/mL. The final sample included 443 eligible women.

Participant characteristics according to clinical site are presented in Table 1. Overall, 42% of women were Caucasian, 48% were African American, and 10% self-reported “other” as race. Thirty-five percent reported Hispanic ethnicity. The following variables differed significantly by study site: racial and ethnic distribution of women by design, age, initial hCG, number of hCG values collected, days of follow up, presence of pain at presentation, gestational age at presentation, and certainty of last menstrual period. Study sites were similar with respect to obstetric history of women and bleeding at presentation.

Figure 2 depicts the predicted hCG curve for resolving pregnancy of unknown location based on the model using all data points contributed by members of the cohort. Values corresponding to the median hCG concentrations are flanked by the 95% and 5% values.

The effect of specific variables on the decline of hCG in miscarriage is presented in Table 2. Demographic and clinical factors that significantly modified the hCG curves included age greater than 35 years ($P=.001$) and pain at initial presentation ($P=.006$). These results, depicted graphically in Figures 3A and 3B show that decline in log-transformed hCG is less rapid in women who are older than 35 years at presentation compared with those younger than 35 years. Conversely, hCG decline was more rapid in women who described pain at presentation compared with those who did not.

Table 3 presents the percent average fall in hCG levels as a function of the initial hCG value across time in our new data compared with what was reported previously by our group (11). The rate of hCG decline is directly proportional to the magnitude of hCG at presentation. On average, with an initial hCG of 2,000 milli-international units/mL and follow up at 2 days, women experience a decline of at least 58%. The comparable 2-day follow-up value in women presenting with an hCG of 5,000 milli-international units/mL was 60%. The average decline in hCG in our new population was slower than previously published (at all initial

hCG concentrations). However, mean and median values of the decline were similar (data not shown).

For the purpose of using these curves to distinguish spontaneous miscarriage from ectopic pregnancy, our focus was on the extremes of the predicted curves (90th percentile and 95th percentile) for each starting hCG that describes the minimum predicted hCG decline and provides a threshold for clinical discrimination. Based on our modeling, the minimum rate of hCG decline at 2 days (95th percentile) of follow-up ranged from 35% to 50% (depending on initial hCG) and ranged from 66% to 87% at 7 days. The values from this analysis are juxtaposed with our previous data in Table 4. Compared with our previously published findings on the decline of hCG in women with miscarriage, these new data demonstrate a greater expected minimum drop for those women considered to have a spontaneously resolved pregnancy of unknown location (ie, the 90th and 95th percentiles of the projected curve). For example, with a starting hCG of 2,000 milli-international units/mL, the curve from 2004 predicted that a minimum decline of 31% (95th percentile hCG value) at 2 days was consistent with spontaneous miscarriage (11) while the updated curve predicts a minimum decline of 46% (95th percentile hCG value) at 2 days in women with a resolved pregnancy of unknown location. The contrast between the curves is less marked at 7 days.

DISCUSSION

The goal of this investigation was to present hCG elimination curves in women with a spontaneously resolved pregnancy of unknown location, derived from an ethnically and geographically diverse population, using innovative methods to derive the curves. The use of linear mixed-effects models to generate an hCG slope and nonlinear mixed-effects models to estimate the shift by each person in the sample better reflects the natural history of the decline in hCG in this population. The updated analyses demonstrated that while the mean hCG fall of a resolving pregnancy of unknown location was slower than previously reported, the threshold (90th or 95th percentile of the project curves) to define when the hCG was not falling “fast enough” to be considered resolved was higher. The difference between the two analyses regarding minimum thresholds to define whether hCG was resolving fast enough (at a given time and given an initial hCG) illustrate the variability of hCG resolution, or could be an artifact of our modeling. Differences between current and prior analyses may be explained by competing factors influencing the generation of hCG by remaining trophoblast and the clearance of hCG and were most pronounced with early hCG follow up (2 days after presentation). Such variability emphasizes the need to exercise caution when interpreting the decline in a woman with a pregnancy of unknown location, especially when values are close to reported minimum thresholds.

In our current analysis, the 95% predictive bound for the minimum hCG decline in women with resolving pregnancy of unknown location ranged from 35% to 50% at 2 days and 66% to 87% at 7 days for starting hCG values of 250–5,000 milli-international units/mL. In our previously published data, the minimum rate of hCG decline that was consistent with miscarriage ranged from 24% to 35% at 2 days and 68% to 84% at 7 days (11). In our study validating the concept of comparing hCG curves of women at risk for ectopic pregnancy to that of expected normal women with resolved pregnancy of unknown location, or viable intrauterine pregnancy, the threshold that misclassified the fewest ectopic pregnancies was an hCG decline of 36–47% at 2 days which is closer to our current estimates (13). However it was noted in that study that a high number of women with miscarriage would have undergone intervention in order to maximize the number of women with ectopic pregnancy diagnosed.

A decline in hCG slower than the predictions we report herein identifies a woman at risk, but does not make the diagnosis of ectopic pregnancy. Continued surveillance is warranted with additional values, especially when a woman remains pain free. The number of instances when the pattern of hCG can mislead a clinician into a false diagnosis can be minimized by obtaining additional values as well as considering the entire clinical situation (13). Even when a pregnancy is considered nonviable, the utilization of interventions such as uterine curettage and methotrexate administration should be reserved for management when clinical indicators accumulated over a reasonable interval suggest an increasing concern for ectopic pregnancy. Thus, the optimal threshold to aid in the diagnosis of ectopic pregnancy and miscarriage is an hCG decline of approximately 35–50% at 2 days but is dependent on the clinical situation including acceptance of intervention.

We also report that clinical and demographic factors affect the decline in hCG (Figure 3). One possible explanation for our findings of more rapid hCG decline in women with a pregnancy of unknown location experiencing pain is that increased clearance of hCG occurs due to greater uterine contractility resulting in extrusion of uterine contents. It is not readily apparent why maternal age should affect hCG elimination curves in a pregnancy of unknown location. The primary determinant of hCG half-life is the carbohydrate content (sialic acid) of the hormone that is directly proportional to its biological activity (14). While it is possible that older women have differential patterns of hCG glycosylation that result in diminished metabolism of the hormone, data supporting this could not be found in the literature. However, because the effects of age and pain on hCG resolution are subtle, and due to the large overlap in hCG values, these variables appear to have limited clinical utility. The most important effect modifier of the hCG decline remains initial hCG value.

The current hCG curves are derived from a population of women that is more diverse, geographically, ethnically and racially, than in our previous report, a major strength of this research. Another strength of our findings is the completeness of data collection that allows for the availability of expected declining hCG levels at multiple time points up to 7 days after presentation.

In summary, we have presented newly derived curves that predict the decline in hCG in women presenting with a pregnancy of unknown location and ultimately diagnosed with a resolved pregnancy of unknown location. Declines less steep at characterized time points warrant further evaluation to differentiate miscarriage from ectopic pregnancy. These updated data, derived from the best methods available should enhance the discriminatory power of the hCG curves to guide clinical care. Ultimately, the rules that define declining hCG in miscarriage must be incorporated into an approach to care that includes best clinical judgment, an appropriate number of serial hCG assessments, and risk factor assessment to provide an accurate and timely final diagnosis for women presenting with a pregnancy of unknown location.

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Figure 1.

Figures 1A and 1B. Predicted minimum human chorionic gonadotropin (hCG) decline and hypothetical patient hCG decline. **X** marks the point at which intervention is necessary to rule out ectopic pregnancy because of suboptimal hCG decline. A. Starting hCG of 2,000 milli-international units/mL. B. Starting hCG of 10,000 milli-international units/mL).

Figure 2.
Modeled human chorionic gonadotropin (hCG) decrease by time.

Figure 3.

A. Comparison of human chorionic gonadotropin (hCG) curve in participants aged 35 years or older compared with those aged less than 35 years (with 95% confidence interval of the predicted curves). B. Comparison of hCG curve in participants with and without pain at presentation (with 95% confidence interval of the predicted curves).

Table 1

Demographic and Clinical Characteristics by Clinical Site.

Characteristic	University of Miami (n=163)	University of Pennsylvania (n=207)	University of Southern California (n=73)	Total (n=443)	P
Mean initial hCG (milli- international units/mL)	1002	493	503	639	<0.001
Number of hCG values collected	2.9 ±1.0	3.6 ±1.2	3.1 ±1.1	3.2 ±1.1	<0.001
Follow-up (d)	9.8 ±7.4	11.4 ±7.3	12.3 ±8.5	10.9 ±7.6	0.03
Maternal age (y)	31.0 ±7.6	26.4 ±7.2	30.8 ±7.9	28.8 ±7.8	<0.001
Age 35 years or older	33.1 (54)	15.5 (32)	35.6 (26)	25.3 (112)	<0.001
Race					<0.001
Caucasian	63.8 (104)	10.1 (21)	86.3 (63)	42.4 (188)	
African American	35.6 (58)	73.4 (152)	4.1 (3)	48.1 (213)	
Other	0.6 (1)	16.4 (34)	9.6 (7)	9.5 (42)	
Hispanic ethnicity	54.0 (88)	2.9 (6)	83.6 (61)	35.0 (155)	<0.001
Prior miscarriage	27.6 (45)	29.5 (61)	21.9 (16)	27.5 (122)	0.5
Prior ectopic pregnancy	4.3 (7)	3.4 (7)	2.7 (2)	3.6 (16)	0.8
Bleeding at presentation	82.8 (135)	82.6 (171)	80.8 (59)	82.4 (365)	0.9
Pain at presentation	79.1 (129)	52.7 (109)	52.1 (38)	62.3 (276)	<0.001
Last menstrual period date available	98.2 (160)	87.4 (181)	95.9 (70)	92.8 (411)	<0.001
Certain last menstrual period date	89.0 (145)	55.6 (115)	37.0 (27)	64.8 (287)	<0.001
Gestational age at presentation (d)	63.9 ±26.1	49.8 ±18.1	62.6 ±54.0	57.5 ±30.9	<0.001

hCG, human chorionic gonadotropin.

Data are mean (± standard deviation) or % (n) unless otherwise specified.

Table 2

Effect of Clinical and Demographic Factors on Human Chorionic Gonadotropin Decline in Resolving Pregnancy of Unknown Location

Risk factor	Chi-square*	P†
African American race	4.4	0.2
Hispanic ethnicity	1.4	0.7
Age older than 35 years	15.9	0.001
History of miscarriage	2	0.6
Bleeding at presentation	3.6	0.3
History of ectopic pregnancy	4.4	0.2
Pain at presentation	12.3	0.006
Current smoker	5.7	0.1

*
For interaction

†
For presence of interaction

Table 3

Expected Mean Percent Decline in Serial Human Chorionic Gonadotropin Values Over Initial Week of Monitoring, Current Data Compared With 2004 Data.*

Initial hCG (milli-international units/mL)	Mean Percent hCG Decline 2 Days Later		Mean Percent hCG Decline 4 D		Mean Percent hCG Decline 7 Days Later	
	Current	2004	Current	2004	Current	2004
250	48%	70%	71%	83%	86%	93%
500	52%	71%	75%	84%	89%	94%
1000	55%	72%	78%	86%	91%	95%
1500	57%	73%	79%	87%	93%	96%
2000	58%	74%	81%	88%	93%	96%
2500	59%	74%	82%	88%	94%	96%
3000	59%	74%	82%	88%	94%	96%
4000	60%	75%	83%	89%	94%	97%
5000	60%	75%	83%	89%	94%	97%

hCG, human chorionic gonadotropin.

* Data from Barnhart KT, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum hCG and spontaneous complete abortion: defining the normal curve. *Obstet Gynecol* 2004;104:975–81.

Table 4
Expected Minimum Percent Decline in Serial Human Chorionic Gonadotropin Values Over the Initial Week of Monitoring, Current Data Compared With 2004 Data *

Initial hCG (milli- international units/ mL)	Percent Decline 2 Days Later				Percent Decline 4 Days later				Percent Decline 7 Days Later			
	Current Model		2004		Current Model		2004		Current Model		2004	
	90 th *	95 th *	90 th	95 th	90 th	95 th	90 th	95 th	90 th	95 th	90 th	95 th
250	34%	35%	36%	21%	55%	52%	56%	44%	69%	66%	72%	60%
500	40%	38%	39%	24%	61%	59%	61%	50%	76%	74%	77%	68%
1000	44%	42%	42%	28%	66%	64%	65%	55%	81%	79%	82%	74%
1500	46%	44%	43%	30%	68%	67%	68%	58%	84%	82%	84%	77%
2000	47%	46%	44%	31%	70%	68%	69%	60%	85%	83%	85%	79%
2500	48%	47%	45%	32%	71%	70%	70%	62%	86%	84%	86%	80%
3000	49%	48%	46%	33%	72%	70%	63%	71%	87%	85%	87%	81%
4000	50%	49%	47%	34%	73%	72%	72%	64%	88%	86%	88%	83%
5000	51%	50%	47%	35%	74%	73%	73%	66%	89%	87%	89%	84%

hCG, human chorionic gonadotropin.

Percent declines in hCG correspond to 90th and 95th percentiles of hCG values from the curve.

* Data from Barnhart KT, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum hCG and spontaneous complete abortion: defining the normal curve. *Obstet Gynecol* 2004;104:975-81.