Human Chorionic Gonadotropin Profile for Women With Ectopic Pregnancy

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OBJECTIVE: To analyze serial human chorionic gonadotropin (hCG) levels in women presenting to the emergency department who were ultimately confirmed to have ectopic pregnancies.

METHODS: Human chorionic gonadotropin levels were obtained over time until definitive diagnosis. To be included, women had to have at least 2 hCG measurements. Human chorionic gonadotropin curves were characterized and their slopes calculated.

RESULTS: Two hundred women received diagnoses of ectopic pregnancy with the help of serial hCG values and were included in the study. No curve adequately characterized the pattern of hCG values so attention was focused on the initial 2 values. The median slope of log hCG among all subjects was 0.11 (25% increase in 2 days). However, 60% of subjects had an initial rise in hCG, and 40% had an initial fall. The rise in hCG for women with ectopic pregnancies (0.28; 75% increase in 2 days) was slower than the mean increase reported for a viable intrauterine pregnancy. The decline in hCG for women with ectopic pregnancies (−0.225; 27% decline in 2 days) was slower than the mean reported for completed spontaneous abortion. However, 20.8% of women presented with a rise in hCG values similar to the minimal rise for women with a viable gestation, and 8% of women presented with a fall in hCG values similar to women with a completed spontaneous abortion.

CONCLUSION: There is no single way to characterize the pattern of hCG for ectopic pregnancy. The number of women with ectopic pregnancy who experience an increase in hCG values is approximately equal to the number of those who experience a decrease. The hCG profile in women with ectopic pregnancy can mimic that of an intrauterine pregnancy or a completed spontaneous abortion in approximately 29% of cases.

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LEVEL OF EVIDENCE: II-2

Ectopic pregnancy is still the leading pregnancy-related cause of death in the first trimester and accounts for 9–13% of all pregnancy-related deaths. Furthermore, the incidence of ectopic pregnancy appears to be increasing and now accounts for 2% of all pregnancies in the United States. This combination of factors shows ectopic pregnancy to be a public health problem.

It is estimated that 30–40 women die each year in the United States from ectopic pregnancies. With these numbers in mind, it is alarming to know that data from emergency departments indicate that 40–50% of women ultimately receiving diagnoses of ectopic pregnancy initially received either diagnoses of some other condition or no diagnosis during their initial visits.

Many factors contribute to the difficulty in confirming the diagnosis. The history of pelvic or abdominal pain and vaginal bleeding is inconsistent among different patients. Clinical examination is usually unrevealing, and positive findings, when present, are lacking in sensitivity and specificity. Finally, nearly 50% of women with an ectopic pregnancy have prior risk factors.

In the vast majority of cases, the diagnosis of ectopic pregnancy is made by using a combination of biochemical and ultrasound parameters. This combination yields a high percentage of correct diagnoses, although, in some cases, the final diagnosis can only be confirmed with anatomicopathologic findings.

When using this combination, we used the concept of an hCG discriminatory zone to aid in the interpretation of ultrasound findings. Below the discriminatory zone, when the positive predictive value
of ultrasonography for detection of intrauterine pregnancies is poor and the initial ultrasound examination is nondiagnostic (no evidence of an intra- or extraterine pregnancy), follow-up serial evaluations of hCG are often used to gain information about the diagnosis and prognosis of early pregnancies.

The hCG curves defining both viable and resolving pregnancies have recently been redefined in women whose initial ultrasound examination was nondiagnostic. A 53% increase in the hCG concentration in 2 days is now considered the lower limit of normal and defines a potentially viable intrauterine pregnancy. The lower limit in the 2-day decline in serial hCG concentration for a completing spontaneous abortion ranges from 21% to 35%, depending on the initial value. Although there is a large amount of additional data in the literature regarding hCG curves for viable and nonviable pregnancies, there is a scarcity of data regarding the behavior of hCG over time for ectopic pregnancies.

By investigating the hCG patterns in patients with symptomatic early pregnancies that ultimately received diagnoses of ectopic pregnancy, we can identify similarities and differences in the profiles of hCG for these gestations. This information will allow clinicians to better predict and manage women at risk for ectopic pregnancy who present with a nondiagnostic ultrasound and are followed up with serial hCG values.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Pennsylvania (Risk Factors as Predictors of Ectopic Pregnancy, #103700). The Hospital of the University of Pennsylvania has a computerized database, dating back to 1990, of all pregnant women presenting to the emergency department in the first trimester with symptoms of pelvic pain and/or vaginal bleeding.

Data were collected from this database for all women who presented between January 1, 1990, and July 31, 1999. For this study, analysis was restricted to women for whom a definitive diagnosis could not be made at their initial visit and who were, therefore, followed up with serial hCG measurements over time until a definitive diagnosis of an ectopic pregnancy was confirmed by anatomopathologic findings. This refers to pathology specimens confirming the presence of products of conception in the fallopian tube or an increase in hCG values after endometrial curetting failed to reveal products of conception in women with no visible intrauterine pregnancy and an initial hCG value above the discriminatory zone or plateauing hCG values below the discriminatory zone.

To be included in the study, women had to have at least 2 hCG measurements, at least 24 hours apart (but no more than 7 days), drawn before the day on which the ectopic gestation was confirmed. Analysis was restricted to only singleton pregnancies. Heterotopic pregnancies were also excluded.

Serum hCG was determined at the Department of Pathology and Laboratory Medicine of the University of Pennsylvania with the Abbott AxSYM (Abbott Laboratories, Abbott Park, IL) or DPC Immulite (Diagnostic Products Corporation, Los Angeles, CA) total β immunoassay. The interassay and intraassay coefficients of variation of these methods were below 10%. Results are expressed as milli-International Units per milliliter (mIU/mL), using the third international reference standard.

We evaluated the serial hCG values, with all analyses being performed on the natural log transformation of hCG values. This transformation was necessary to alleviate the skewness of the hCG distribution and reduce the influence of large values. All hCG values for each individual subject were plotted, and, using graphical methods and semiparametric and parametric random effects models, we attempted to determine the overall shape of the hCG curve for all ectopic pregnancies as a group.

Because the overall shape of the curve could not be adequately characterized by any of the models, we focused on the initial first 2 hCG measurements. The change in hCG levels between the first 2 subsequent measurements was characterized by the slope, which was estimated by the difference in the log hCG levels divided by the observed time between measurements, implying a start time of “0” for the first hCG. After the slopes of the curves were calculated, they were stratified by percentiles.

Subjects were split into 2 groups: those with an initial positive slope (rising hCG values) and those with an initial negative slope (declining hCG values). Clinical characteristics of the women in these 2 groups were compared by using the Student t test or χ² test, as appropriate.

Finally, the percentiles of projected slopes for women with ectopic pregnancies were compared with the percentiles of the slopes for women with potentially viable intrauterine pregnancies or completed miscarriages. The projected frequency that the hCG rise (or fall) for women with ectopic pregnancy would be within the range expected for a viable intrauterine pregnancy or a completed abortion was calculated.

RESULTS

There were 424 cases of ectopic pregnancy in the data set. Of these, 11 were excluded because their diagnoses were known before presentation for care, and 166 were...
excluded because their ectopic pregnancies were diagnosed at the time of their initial presentation. If a woman presented for care for more than one pregnancy during the time period studied, a single record was randomly selected for inclusion in the analysis; 47 ectopic pregnancies were excluded for this reason. This left 200 patients to be included in the present analysis.

The mean age of the population was 27.34 years, with an average gravity and parity of 2.1 and 0.72, respectively. A total of 85% of the population was African American, 12% were white, and 3% other. Descriptive statistics, including mean gestational age at presentation, the number of visits per patient, days until diagnosis, and starting \( \beta \)-hCG values, are presented in Table 1.

During evaluation of curves generated from the serial hCG values, we observed that no model could adequately characterize the pattern of serial hCG values from women with ectopic pregnancy. Some women had a rise in hCG, whereas others had declining or plateauing hCG values. Figure 1 shows examples of different individual hCG profiles. Because diagnosis of women at risk for ectopic pregnancy compares 2 values of hCG, we focused on the assessment of the slope of the curves based on the initial 2 subsequent hCG values.

The slopes of the hCG curves generated by all women with ectopic pregnancy, stratified by percentiles, are presented in Table 2. The median slope of \( \log \beta \)-hCG for a woman with an ectopic pregnancy was 0.11 (or a 25% increase in 2 days). However, 5% of women with an ectopic pregnancy had slopes as fast as 0.83 (a 426% increase in 2 days) or a fall of −0.68 (a decrease of 74% in 2 days).

We then divided the population into 2 groups: those with an initial rise in hCG and those with an initial decline in hCG. Of the 200 patients who received diagnoses of ectopic pregnancy, 60% (n = 121) initially presented with rising hCG values (Group A), and 40% (n = 79) initially presented with declining hCG values (Group B).

The descriptive statistics of patients in these 2 groups are presented in Table 3. The group of women who presented with a rising hCG level presented for care with a significantly lower mean hCG concentration (700.36 versus 1,287.68 mIU/mL, \( P < .006 \)). They also tended to present at an earlier mean gestational age (38.96 versus 42.72 days, \( P < .19 \)), although this was not statistically significant. However, the mean number of visits made (3.53 versus 3.51, respectively, \( P < .93 \)) and the mean number of days required (5.34 versus 5.29, \( P < .72 \)) to confirm the diagnosis were similar between the 2 groups.

The slope and percentiles for the rate of increase (and decrease) were calculated for each group and are presented in Table 4. The median (50%) slope of the curve for women with ectopic pregnancy and an initial rise in hCG was 0.278 (or a 75% increase in 2 days). This slope of increase is less (slower) than the mean rise of 2.24 (or a 124% rise) previously described for a viable intrauterine pregnancy. The median 2-day slope for women with ectopic pregnancy and an initial decline in hCG was −0.225 (or a 27% decline in 2 days). This decline is less (slower) than the mean decline of 72% previously described for a completed spontaneous miscarriage starting with an hCG of 1,000 mIU/mL.

Finally, we evaluated how often a woman with an ectopic pregnancy would have a slope that would mimic that of a potentially viable intrauterine pregnancy or a

Table 1. Descriptive Statistics of All Patients Ultimately Diagnosed With Ectopic Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of visits</td>
<td>3.52</td>
<td>3.00</td>
<td>1.75</td>
</tr>
<tr>
<td>Days to diagnosis</td>
<td>5.32</td>
<td>4.00</td>
<td>4.89</td>
</tr>
<tr>
<td>( \beta )-hCG at presentation (mIU/mL)</td>
<td>932.35</td>
<td>418.50</td>
<td>1,488.44</td>
</tr>
<tr>
<td>( \beta )-hCG at diagnosis (mIU/mL)</td>
<td>1,233.57</td>
<td>517.50</td>
<td>1,802.68</td>
</tr>
<tr>
<td>EGA at presentation (d)</td>
<td>40.47</td>
<td>40.00</td>
<td>19.43</td>
</tr>
<tr>
<td>EGA at diagnosis (d)</td>
<td>45.84</td>
<td>45.00</td>
<td>19.53</td>
</tr>
<tr>
<td>Log ( \beta )-hCG at presentation</td>
<td>6.05</td>
<td>6.04</td>
<td>1.27</td>
</tr>
<tr>
<td>Log ( \beta )-hCG at diagnosis</td>
<td>6.29</td>
<td>6.25</td>
<td>1.38</td>
</tr>
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</table>

SD, standard deviation; EGA, estimated gestational age.

resolving completed abortion. The slope of the curve for the first percentile for intrauterine pregnancies represents a 53% increase in hCG value in 2 days. In other words, hCG will rise this fast or faster in 99% of the viable intrauterine pregnancies. The slope of the curve for the 95th percentile for completed spontaneous abortion starting with an hCG of 1,000 mIU/mL represents a 28% decline in 2 days. In other words, hCG will decline this fast or faster in 95% of completed spontaneous abortions that started with an hCG of 1,000 mIU/mL. In our previous studies, a stringent 99% confidence interval (CI) was presented to limit the possibility of interrupting a viable intrauterine pregnancy. A 95% CI was presented to characterize the curve of a completed abortion because the trade-off between the errors of delayed diagnosis of an ectopic pregnancy and unnecessary intervention for a completed miscarriage was not as unbalanced.

When comparing the slopes of the hCG curves of women with ectopic pregnancy with those previously defined, we noted a considerable overlap. Of those women with ectopic pregnancy, 20.8% were noted to have a rate of increase in hCG as fast or faster than the curve defining the first CI for a viable gestation. Similarly, 8% of the women with an ectopic pregnancy had a decline in hCG that was as fast or faster than the slope defining the 95% CI for women with a completed abortion (with an initial hCG value of 1,000 mIU/mL).

<table>
<thead>
<tr>
<th>Percentile</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>85</th>
<th>90</th>
<th>95</th>
<th>99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope*</td>
<td>-1.16</td>
<td>-0.68</td>
<td>-0.48</td>
<td>-0.27</td>
<td>-0.12</td>
<td>0.11</td>
<td>0.36</td>
<td>0.57</td>
<td>0.63</td>
<td>0.83</td>
<td>1.19</td>
</tr>
<tr>
<td>Two-day change† (%)</td>
<td>-90</td>
<td>-74</td>
<td>-62</td>
<td>-21</td>
<td>-13</td>
<td>25</td>
<td>105</td>
<td>213</td>
<td>253</td>
<td>426</td>
<td>980</td>
</tr>
</tbody>
</table>

* Slope represents the change in log hCG expected for the first 2 visits, including presentation for care.
† Two-day change represents the relative 2-day decrease or increase in hCG (mIU/mL). Computed as exp (slope × 2).

Table 2. Change in Serial Human Chorionic Gonadotropin (hCG) for Women With Ectopic Pregnancy, by Percentiles

<table>
<thead>
<tr>
<th>Percentile</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>85</th>
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<tr>
<td>Slope*</td>
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<td>0.68</td>
<td>0.48</td>
<td>0.27</td>
<td>0.12</td>
<td>0.11</td>
<td>0.36</td>
<td>0.57</td>
<td>0.63</td>
<td>0.83</td>
<td>1.19</td>
</tr>
<tr>
<td>Two-day change† (%)</td>
<td>90</td>
<td>74</td>
<td>62</td>
<td>21</td>
<td>13</td>
<td>25</td>
<td>105</td>
<td>213</td>
<td>253</td>
<td>426</td>
<td>980</td>
</tr>
</tbody>
</table>

* Slope represents the change in log hCG expected for the first 2 visits, including presentation for care.
† Two-day change represents the relative 2-day decrease or increase in hCG (mIU/mL). Computed as exp (slope × 2).

Table 3. Descriptive Statistics of Patients With Ectopic Pregnanies With Rising (Group A) and Declining (Group B) hCG Values

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 121)</th>
<th>Group B (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Number of visits</td>
<td>3.53</td>
<td>3.00</td>
</tr>
<tr>
<td>Days to diagnosis</td>
<td>5.34</td>
<td>4.00</td>
</tr>
<tr>
<td>β-hCG at presentation (mIU/mL)</td>
<td>700.36</td>
<td>384.00</td>
</tr>
<tr>
<td>β-hCG at diagnosis (mIU/mL)</td>
<td>1,391.55</td>
<td>696.00</td>
</tr>
<tr>
<td>EGA at presentation (d)</td>
<td>38.96</td>
<td>39.00</td>
</tr>
<tr>
<td>EGA at diagnosis (d)</td>
<td>44.30</td>
<td>44.00</td>
</tr>
</tbody>
</table>

SD, standard deviation; EGA, estimated gestational age.

Table 4. Change in Serial Human Chorionic Gonadotropin (hCG) for Women With Ectopic Pregnancy, Stratified by Group

<table>
<thead>
<tr>
<th></th>
<th>Percentile</th>
<th>Group A (n = 121)</th>
<th>Group B (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope*</td>
<td>0.120</td>
<td>0.278</td>
<td>0.563</td>
</tr>
<tr>
<td>Two-day change† (%)</td>
<td>27</td>
<td>75</td>
<td>206</td>
</tr>
</tbody>
</table>

* Slope represents the change in log hCG expected for the first 2 visits, including presentation for care.
† Two-day change represents the relative 2-day decrease or increase in hCG (mIU/mL). Computed as exp (slope × 2).
with a profile that would be consistent with a completed spontaneous abortion.

**DISCUSSION**

This study completes the objective of characterizing hCG profiles in a large cohort of patients with symptomatic early pregnancy of unknown location whose diagnosis could not be made at presentation.\(^8,9\) This study was not designed to address the diagnosis of all women with ectopic pregnancy. The focus of this study was the hCG pattern of women with ectopic pregnancy whose initial diagnosis was unclear and for whom serial hCG values were used to aid in final diagnosis. This is a common situation faced by clinicians who care for women in the first trimester of pregnancy.

In recent years there has been a significant improvement in the diagnosis of ectopic pregnancy because of the introduction of the concept of an hCG discriminatory zone and improved ultrasound techniques. To further aid in diagnosis, we have characterized the rise of a viable intrauterine gestation and the decline in a completed abortion. Attention is now focused on women with ectopic pregnancy. Although there is anecdotal knowledge about these patterns of hCG in ectopic pregnancy, one of the strengths of this paper is that we have evaluated a large cohort of patients with ectopic pregnancy whose initial hCG values started below the discriminatory zone, where evaluation of serial hCG values is the standard of care. The systematic evaluation of a large series of patients will provide evidence for the guidelines used during outpatient surveillance of women at risk for ectopic pregnancy. A prompt diagnosis, before tubal rupture, not only allows for treatment but also minimizes complications and risks to future fertility.

Despite the fact that many hCG values were obtained for each patient, we found that there was no single way to characterize the pattern of hCG for ectopic pregnancies diagnosed by using hCG surveillance. This is an important point in itself because it is in contrast to the curves derived from women with ongoing pregnancies or completed spontaneous abortions.\(^8,9\)

Since the “overall shape” of the curve could not be determined, we chose to focus on the first 2 hCG values to calculate the slope of the curves. Currently, evaluation of 2 consecutive hCG values is the standard of care in the diagnosis of women at risk for ectopic pregnancy. If the values are rising or falling “normally,” the next 2 values are compared. This logic continues until the hCG curve is outside of that expected, the patient becomes symptomatic, a definitive diagnosis is made by ultrasonography, or hCG is no longer detectable in the serum. We chose to use the first 2 hCG values because these first 2 data points are frequently the greatest clinical conundrum faced by physicians and because these 2 values represent the most complete data.

In our series, we noted that 60% of the patients presented with rising hCG and 40% with declining hCG values. In comparing patients who presented with rising hCG values (group A) with patients presenting with declining hCG values (group B), the only statistically significant difference encountered was that the former had lower hCG values at their initial visit. The reason for this finding is not clear, but it may be related to the fact that women in this group tended to present at earlier gestational ages. Although the difference was not statistically significant, this could be the result of nondifferential measurement error in the estimated gestational age. We recognize that our sample is from an inner-city setting with a predominance of African-American women, thus limiting generalizability.

Upon evaluation of the slope of the first 2 values, we noted that the median slope for patients with ectopic pregnancies and rising hCG values was 0.278 (or a 75% increase in hCG in 2 days), which is slower than the mean increase for an intrauterine pregnancy (124%).\(^8\) Additionally, the median slope of the curve for patients with ectopic pregnancies and declining hCG was \(-0.225\) (or a 27% decline in hCG in 2 days), which was slower than the mean decline for a completed spontaneous abortion (70–75%).\(^9\) Thus, these data confirm that, as a population, the predictable rise in hCG of a viable intrauterine pregnancy is distinct from the slow rise, plateau, or drop of hCG of a nonviable pregnancy, such as an ectopic pregnancy or miscarriage. Moreover, the decline of hCG for an ectopic pregnancy, in general, is slower than that of a miscarriage.

It is reassuring that from these data we can infer that the majority (approximately 71%) of patients with ectopic pregnancies will have a change in their hCG levels between the first and second samples that is outside the normal range for either a viable intrauterine pregnancy or a completed spontaneous abortion. Therefore, when the diagnosis is unclear, serial hCG measurements can be used to identify a population at much higher risk for ectopic pregnancy. Importantly, however, there is considerable overlap when looking at individual cases. Also important is that one hCG value is of no use to distinguish a viable intrauterine pregnancy, a spontaneous miscarriage, or an ectopic pregnancy.

These data suggest that, when following a patient with a symptomatic early pregnancy (pelvic pain and/or vaginal bleeding), a “normal” hCG rise (53% increase in 2 days) alone does not confirm the presence of an
intrauterine pregnancy. Instead, that increase describes the lower boundary of a gestation that has the potential to be a viable intrauterine pregnancy. Gestations that have an hCG increase of 53% (or more) in 2 days can still be ectopic pregnancies. In fact, we demonstrate that one third of ectopic pregnancies can have this rise (or a faster rise). This represents 20% of all women who presented with an ectopic pregnancy in our series. Therefore, patients with an increase in hCG should continue to be followed until a definite intrauterine pregnancy is confirmed by ultrasound examination. These data also demonstrate that the diagnosis of a woman at risk for ectopic pregnancy cannot rely solely on a single diagnostic test, such as serial hCG values. It is necessary to evaluate all of the clinical data, laboratory values, and ultrasound findings to guide diagnosis and treatment.

Similarly, women with an ectopic pregnancy can have a decline in hCG that is similar to that in women with a completed spontaneous miscarriage. Our data demonstrate that 21% of all women with ectopic pregnancy who had initially declining hCG values had a decline as fast (or faster) than the recently defined upper limit of decline for women with completed miscarriages. This represents 8% of all women who presented with ectopic pregnancy in our series. Therefore, women with ectopic pregnancy who initially presented with declining hCG values that could be considered “normal” for completed spontaneous abortion still require close follow-up.

The clinical implications of our findings are considerable. The inherent overlap of the curves for intrauterine pregnancy, ectopic pregnancy, and completed spontaneous abortion underscores the importance of taking into consideration other diagnostic tests. Serial hCG observations cannot rule out with 100% sensitivity and specificity the presence or absence of an ectopic pregnancy. Care must be taken to use all diagnostic methods available to make the diagnosis of ectopic pregnancy in a stable patient in a timely fashion, without interrupting a desired intrauterine pregnancy or providing false reassurance to a patient that she is not at risk for an ectopic pregnancy (and potential rupture).

REFERENCES