ORIGINAL ARTICLE: EARLY PREGNANCY

Human chorionic gonadotropin discriminatory zone in ectopic pregnancy: does assay harmonization matter?

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Objective: To determine the effect that lack of hCG assay harmonization has on the interpretation of a serum hCG concentration with regards to the hCG discriminatory zone.
Design: A multisite method comparison study.
Setting: Clinical laboratories.
Patient(s): Eighty serum samples containing various concentrations of hCG.
Intervention(s): None.
Main Outcome Measure(s): Concentrations of hCG obtained from seven hCG reagent platforms.
Result(s): The hCG concentrations were significantly different across hCG reagent platforms. Seventy-one percent of assay pairs showed significant differences with samples selected based on hCG concentrations between 1,500 and 3,500 IU/L as determined by a comparative method. Relative to the comparative method, the calculated hCG discriminatory zones for five assays were within 9%, and one assay was within 40% of the target concentrations of 1,500 and 3,500 IU/L.
Conclusion(s): Despite significant differences in hCG concentrations across hCG immunoassays, an hCG concentration within a discriminatory zone of 1,500–3,500 IU/L can be used for all but one commonly used hCG reagent platform. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Ectopic pregnancy, hCG, hCG discriminatory zone, harmonization

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Ectopic pregnancy is a potentially life-threatening complication of pregnancy in which the embryo implants outside the uterine cavity, most commonly in the fallopian tube. It frequently presents as abdominal pain and may result in vaginal bleeding. The incidence of ectopic pregnancy is approximately 2% of all pregnancies, and it is the leading cause of maternal mortality in the first trimester (1). Consequently, prompt and accurate diagnosis of an ectopic pregnancy is of high importance.

Diagnosis of an ectopic pregnancy requires the exclusion of a normal, intrauterine pregnancy and is facilitated by the use of transvaginal ultrasound (TVUS) to visualize the location of the yolk sac or embryo. If present, an intrauterine pregnancy should be evident by TVUS at $\geq$42 days of gestation (1). However, such precise dating is often not available for patients who present with symptoms of ectopic pregnancy and a nondiagnostic TVUS. For these patients, the concentration of serum hCG is used as a surrogate marker for gestational age and is commonly interpreted against the "hCG discriminatory zone," the concentration of hCG at which the sensitivity of TVUS for detecting an

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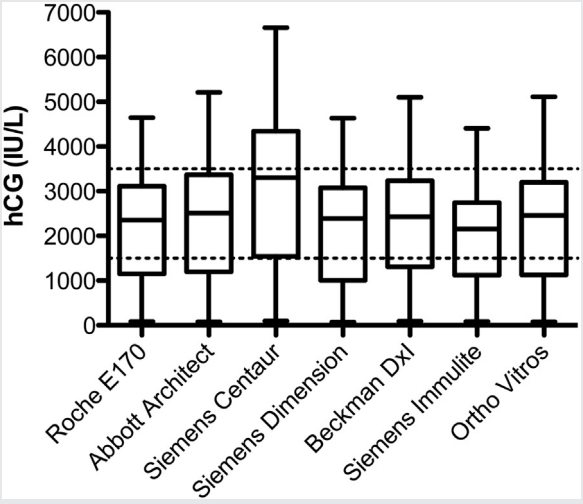
FIGURE 1



Box and whisker plot of hCG results from 80 serum samples tested on seven commercially available hCG platforms. The whiskers represent the minimum and maximum hCG result, and the horizontal bar in the box represents the median. The *dashed lines* represent the hCG discriminatory zone of 1,500–3,500 IU/L. See text for the name of the hCG assay used on each platform.

Desai. hCG discriminatory zone and assay harmonization. Fertil Steril 2014.

intrauterine gestation is nearly 100% (1). The absence of an intrauterine gestation when the hCG concentration exceeds the discriminatory zone suggests that the pregnancy is not viable, but it is not diagnostic of an ectopic pregnancy (2). The hCG discriminatory zone is commonly described as an hCG cutoff concentration between 1,500 and either 2,000, 2,500 or 3,000 IU/L. Guidelines from the American College of Obstetricians and Gynecologists define it as 1,500–2,000 IU/L (3).

Importantly, quantitative hCG assays are not harmonized, meaning that hCG results from different reagent platforms can yield different results when the same sample is tested. Clinical practice guidelines that recommend specific analyte concentrations as decision thresholds often fail to address the effect that the lack of harmonization can have on result interpretation. The objective of this study was to determine the effect that the lack of hCG assay harmonization has on the interpretation of an hCG result with regards to the hCG discriminatory zone.

MATERIALS AND METHODS

Deidentified, residual serum samples sent to ARUP Laboratories for hCG testing were used for this study with approval from the University of Utah Institutional Review Board. Samples were selected based on hCG concentration and were used to create, by pooling if necessary, 80 discrete specimens. By design, 25% of the samples were created to target an hCG concentration <1,000 IU/L, 50% with an hCG concentration between 1,000 and 4,000 IU/L, and 25% with an hCG concentration of >4,000 IU/L. After preparation, 0.5 mL aliquots were prepared and the samples stored at −20°C or colder until they were tested up to 7 days later.

The concentration of hCG in each sample was determined using each of the following commercially available hCG assays: ARCHITECT Total β-hCG (Abbott Diagnostics), DxI Total hCG (Beckman Coulter Diagnostics), E170 hCG+β (Roche Diagnostics), Centaur Total hCG (Siemens Healthcare Diagnostics), Dimension hCG (Siemens Healthcare Diagnostics), IMMULITE hCG (Siemens Healthcare Diagnostics), and Vitros 5600 β-hCG (Ortho Clinical Diagnostics). Each of these assays recognizes intact hCG and several hCG variants with no cross-reactivity with other glycoprotein hormones. Across all assays, coefficients of variation ranged from a low of 2.3% at 1,780 IU/L to 5.5% at 365 IU/L. A minimum of two quality-control materials were evaluated before sample testing to verify acceptable analytical performance. Statistical analysis was performed using nonparametric repeated measures analysis of variance followed by post hoc testing to compare pairs of group means (n = 21 pairs). Deming regression was used to define the relationship between each assay and the comparative method. The Roche E170 assay was selected as the comparative method because it detects all clinically relevant forms of serum hCG with equimolar detection (4, 5). Statistical analyses were performed using Prism (version 5, GraphPad Software).

TABLE 1

Post hoc testing after nonparametric repeated measures analysis of variance to compare group means from serum samples tested on seven commercially available hCG platforms.

	Abbott Architect	Beckman DxI	Siemens Centaur	Siemens Dimension	Siemens Immulite	Ortho Vitros	Roche E170
Beckman DxI	<0.05						
Siemens Centaur	<0.05	<0.05					
Siemens Dimension	<0.05	<0.05[a]	<0.05				
Siemens Immulite	<0.05	<0.05	<0.05	NS[b]			
Ortho Vitros	<0.05	NS	<0.05	NS	<0.05		
Roche E170	<0.05	NS	<0.05	NS	<0.05	NS	

Note: See text for the name of the hCG assay used on each platform. NS = not significant.

[a] This pair was not significantly different using 43 serum samples selected on the basis of an hCG concentration between 1,500 and 3,500 IU/L as determined by the comparative method.

[b] This pair was significantly different ($P<.05$) using 43 serum samples selected on the basis of an hCG concentration between 1,500 and 3,500 IU/L as determined by the comparative method.

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