Further Evidence Against the Reliability of the Human Chorionic Gonadotropin Discriminatory Level

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Objectives—The human chorionic gonadotropin (hCG) discriminatory level—the maternal serum β-hCG level above which a gestational sac should be consistently visible on sonography in a normal pregnancy—has been reported to be 1000 to 2000 mIU/mL for transvaginal sonography. We assessed whether a woman with a β-hCG above 2000 mIU/mL and no intrauterine fluid collection on transvaginal sonography can subsequently be found to have a live intrauterine gestation and, if so, what the prognosis is for the pregnancy.

Methods—We identified all women scanned between January 1, 2000, and December 31, 2010, who met the following criteria: serum β-hCG testing and transvaginal sonography were performed on the same day; β-hCG was positive and sonography showed no intrauterine fluid collection; and a live intrauterine pregnancy was subsequently documented. We tabulated the β-hCG levels in these cases and assessed pregnancy outcome.

Results—A total of 202 patients met the inclusion criteria, including 162 (80.2%) who had β-hCG levels below 1000 mIU/mL on the day of the initial scan showing no intrauterine fluid collection, 19 (9.4%) with levels of 1000 to 1499, 12 (5.9%) 1500 to 1999, and 9 (4.5%) above 2000 mIU/mL. There was no significant relationship between initial β-hCG level and either first-trimester outcome or final pregnancy outcome ($P > .05$, logistic regression analysis and Fisher exact test). The highest β-hCG was 6567 mIU/mL, and the highest value that preceded a liveborn term baby was 4336 mIU/mL.

Conclusions—The hCG discriminatory level should not be used to determine the management of a hemodynamically stable patient with suspected ectopic pregnancy, if sonography demonstrates no findings of intrauterine or ectopic pregnancy.

Key Words—discriminatory level; ectopic pregnancy; human chorionic gonadotropin; sonography

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Abbreviations

hCG, human chorionic gonadotropin; IRP, International Reference Preparation; IS, International Standard

A complex sequence of events occurs in early pregnancy, beginning almost immediately after fertilization. Through innumerable cell divisions, what starts as a single cell—the zygote—grows into a multicellular structure that includes the embryo and gestational sac. Simultaneously, chemical changes take place to help support the developing pregnancy, including production of the hormone human chorionic gonadotropin (hCG) by the syncytiotrophoblasts of the developing placenta. In a normal pregnancy, the structural and chemical processes occur in parallel, so that the hCG concentration in the mother's blood correlates fairly closely with the size and development of the gestational sac and embryo.

The gestational sac can usually be seen by transvaginal sonography once it reaches 2 to 5 mm in diameter, which occurs at approximately 5 weeks' gestational age (ie, 3 weeks after conception). Factors such as resolution of the ultrasound scanner, maternal body habitus, uterine orientation, and presence or absence of fibroids all affect when, and at what size, the sac becomes visible. The early gestational sac appears on sonography as a fluid collection in the central echogenic portion of the uterus. In some cases the gestational sac displays the "double sac sign"[1] or the "intradecidual sign,"[2] but in many cases neither of these sonographic signs is present and the sac appears as a "nonspecific" fluid collection in the mid-uterus.[3]

Starting in the early 1980s, several authors tried to determine the maternal serum hCG level above which a gestational sac should be consistently visible on sonography in a normal intrauterine pregnancy, a value termed the hCG "discriminatory zone" (or "discriminatory level").[4] For transvaginal sonography, the discriminatory level was reported by some authors to be 1000 mIU/mL,[5,6] by others 1500 mIU/mL,[7,8] and by still others 2000 mIU/mL.[9] (Note: serum hCG levels are measured as the concentration of the β subunit of hCG, or β-hCG, via the first International Reference Preparation [IRP], second International Standard [IS], third IS, or fourth IS. The second IS yields results that are approximately half the numeric values of the other three methods. In this paper, unless otherwise specified, all hCG values that we report are applicable to the first IRP, third IS, or fourth IS).

The original rationale for the hCG discriminatory level was that it would aid in the management of a woman presenting with pain and/or bleeding in early pregnancy: if her serum β-hCG is above the discriminatory level and no intrauterine gestational sac is seen on sonography, then it should be safe to treat her for suspected ectopic pregnancy without fear of damaging a normal intrauterine pregnancy. This rationale, however, has been thrown into some doubt by at least one study suggesting that the discriminatory level is not completely reliable.[10] In particular, that study found that a woman with a β-hCG above 2000 mIU/mL and a transvaginal sonogram that shows no intrauterine gestational sac will occasionally have a normal intrauterine pregnancy on a follow-up sonogram. In that study, an intrauterine fluid collection was considered to represent a gestational sac only if it demonstrated an intradecidual sign or contained a yolk sac or embryo.

Since it is common for an early pregnancy to appear as a nonspecific intrauterine fluid collection, without a yolk sac or embryo or features of an intradecidual sign, we performed a study to answer the following questions: Can an early pregnancy with a β-hCG above 2000 mIU/mL and no intrauterine fluid collection seen on transvaginal sonography develop into a live intrauterine gestation? If so, what is the prognosis for these pregnancies, and how high can the β-hCG be in a woman with an apparently empty uterus who goes on to develop a live embryo or fetus?

Materials and Methods

Our study was approved by our Institutional Review Board. We reviewed our ultrasound and hospital databases to identify all women scanned at our institution between January 1, 2000, and December 31, 2010, who met the following criteria: serum β-hCG testing (third or fourth IS) and transvaginal sonography were performed on the same day; the β-hCG was positive and sonography showed no intrauterine fluid collection; and a live intrauterine pregnancy was subsequently documented on a follow-up sonogram showing embryonic or fetal cardiac activity.

Our protocol for scanning women in early pregnancy includes both transabdominal and transvaginal imaging, the latter using broadband transducers with frequencies of 5 to 9 MHz. Images and video clips of the entire uterus and both adnexal regions are stored. Scans are generally performed by a sonographer, and are interpreted by a sonologist who subspecializes in sonography or emergency radiology. The sonologist is most often in the scanning room for at least part of the transvaginal examination, and in all cases reviews the stored images and video clips when interpreting the study.

We tabulated the β-hCG levels in the study cases to determine the number of cases in which the β-hCG was below 1000, between 1000 and 1499, between 1500 and 1999, and at or above 2000 mIU/mL. For cases with β-hCG at or above 2000 mIU/mL, we retrieved and examined the stored images and clips to assess the quality of the scan and determine whether the endometrium had been well seen.

Based on review of each patient's medical record, we categorized the first-trimester outcome as "live" if there was either a live birth or a second- or third-trimester scan showing cardiac activity, "demise" if there was a first-trimester scan showing spontaneous demise or a note in the medical record documenting a miscarriage, and "uncertain" otherwise. We categorized final pregnancy outcome as "liveborn" if a live baby was delivered after 25 weeks' gestation, "demise" if there was a spontaneous pregnancy loss at any gestational age, and "uncertain" otherwise. We assessed the relationship between initial hCG level and first-trimester and final pregnancy outcomes using the Fisher exact test and logistic regression.

Results

Over the 11-year time period, 202 patients met the inclusion criteria for our study: a transvaginal sonogram showing no intrauterine fluid collection on the same day as a positive β-hCG, and subsequent documentation of a living intrauterine embryo or fetus on follow-up sonography. Of these, 194 (96.0%) had a live singleton gestation and 8 (4.0%) had a live twin gestation subsequently documented.

Twenty-eight of the study cases had "uncertain" first-trimester outcome. Of the remaining 174 cases, 156 (89.7%) were alive at the end of the first trimester, and 18 (10.3%) had a spontaneous first-trimester pregnancy loss. Among 158 cases with known final pregnancy outcome, 135 (85.4%) were liveborn.

Among all 202 study cases, 162 (80.2%) had β-hCG levels below 1000 mIU/mL on the day of the initial scan showing no intrauterine fluid collection, 19 (9.4%) had β-hCG levels of 1000 to 1499, 12 (5.9%) had β-hCG levels of 1500 to 1999, and 9 (4.5%) had β to hCG levels at or above 2000 mIU/mL. There was no significant relationship between initial hCG level and outcome, as determined by logistic regression analysis using hCG as the independent variable and first-trimester outcome as the dependent variable, or hCG as the independent variable and final pregnancy outcome as the dependent variable (excluding cases with uncertain outcomes) ($P > .05$, both comparisons). Comparing outcomes in cases with β-hCG below 1000 versus above 1000 mIU/mL also showed no significant difference: 89.9% (125 of 139) live at the end of the first trimester in the low hCG group versus 88.6% (31 of 35) live in the high hCG group; 86.6% (110 of 127) liveborn in the low hCG group versus 80.6% (25 of 31) liveborn in the high hCG group ($P > .05$ for both comparisons, Fisher exact test).

Table 1. Study Cases With β-hCG Above 2000 mIU/mL

β-hCG, mIU/mL[a]	Last Available Follow-up
2215	Term liveborn singleton
2217	Term liveborn dichorionic diamniotic twins
2374	Term liveborn singleton
2530	Live singleton on 21-wk scan, then developed chorioamnionitis leading to pregnancy loss
2539	Term liveborn singleton
2993	Term liveborn singleton
4336	Term liveborn singleton
4476	Alive with large subchorionic hematoma on 7.6-wk scan, went on to first-trimester pregnancy loss
6567	Alive with slow heartbeat on 7.1-wk scan, then demise on 8-wk scan

[a]Drawn on the same day as sonography that showed no intrauterine fluid collection.

On review of the sonograms in the 9 patients with β-hCG levels of at least 2000 mIU/mL, we found that all scans were adequate and complete, and none had fibroids or other anatomic features that interfered with visualization of the endometrium. Follow-up information about this group of patients is presented in Table 1. Seven of the 9 were live at the end of the first trimester, and 6 delivered term liveborn babies. The highest β-hCG was 6567 mIU/mL, and the highest value that preceded a liveborn term baby was 4336 mIU/mL. Two study cases with β-hCG above 2000 are depicted in Figures 1 and 2.

Discussion

The term "discriminatory hCG zone" was coined by Kadar et al in 1981 when they published a study assessing the visibility of a normal intrauterine pregnancy on sonography in relation to the hCG level.[4] They found that all normal intrauterine pregnancies in their study population were visible on sonography when the hCG was 6500 mIU/mL (second IS) or above, and no normal intrauterine pregnancy was visible when the hCG was below 6000 mIU/mL. The scans were all performed transabdominally, the standard approach to pelvic sonography at that time. Based on these findings, they called the range of 6000 to 6500 mIU/mL the "discriminatory hCG zone" and concluded that "the absence of a gestational sac above this level [6500 mIU/mL] signifies ectopic pregnancy."

Subsequent studies have focused mainly on the upper end of the discriminatory zone—the hCG value above which an intrauterine pregnancy should always be visible on sonography—because of its potential role in patient management. As the resolution of sonography has improved, permitting visualization of an intrauterine gestational sac earlier in pregnancy, the discriminatory hCG level has been set progressively lower. By 1985, it was reported to be 3600 mIU/mL[11] (listed as 1800 mIU/mL via the second IS in that paper, which is equivalent to 3600 mIU/mL via first, third, or fourth IS). It was further decreased with the advent of transvaginal sonography in the late 1980s, when it has variously reported to be 1000, 1500, or 2000 mIU/mL.[5–9]

Numerous book chapters and review articles attribute an important role to the hCG discriminatory level in the management of women with suspected ectopic pregnancy,[12–17] with statements such as "if it [an intrauterine gestational sac] is not [visible on transvaginal sonography once the β-hCG level is above 1000 mIU/mL], then the

possibilities are either that the products of conception have recently passed or that there is an ectopic pregnancy."[15] Partly as a result of such publications, many emergency departments employ protocols in which a woman with an hCG level above 1500 or 2000 mIU/mL and no sonographically visible intrauterine gestation is presumed to have an ectopic pregnancy or a failed intrauterine pregnancy, and is managed accordingly: either systemic methotrexate[18,19] or dilatation and curettage followed by treatment for ectopic pregnancy if no chorionic villi are present.[20–22] These management approaches would damage an intrauterine pregnancy but, as stated by one of the advocates, "using this cutoff [2000 mIU/mL] as opposed to 1000 mIU/mL . . . gives some leeway so that no viable intrauterine pregnancies are terminated."[18]

Our study indicates, however, that the hCG discriminatory level is not reliable for excluding a normal intrauterine pregnancy. We found that, even in the setting of a transvaginal sonogram showing no intrauterine fluid collection and a β-hCG level above 4000 mIU/mL (more than double the highest reported discriminatory level for transvaginal sonography), a subsequent scan can demonstrate an embryo with cardiac activity, and a live birth can result. Furthermore, if a woman has an initial scan showing no intrauterine fluid collection and is subsequently shown to have a live intrauterine pregnancy, the likelihood that the fetus will survive the first trimester and that the pregnancy will result in a liveborn baby is unrelated to the initial hCG level.

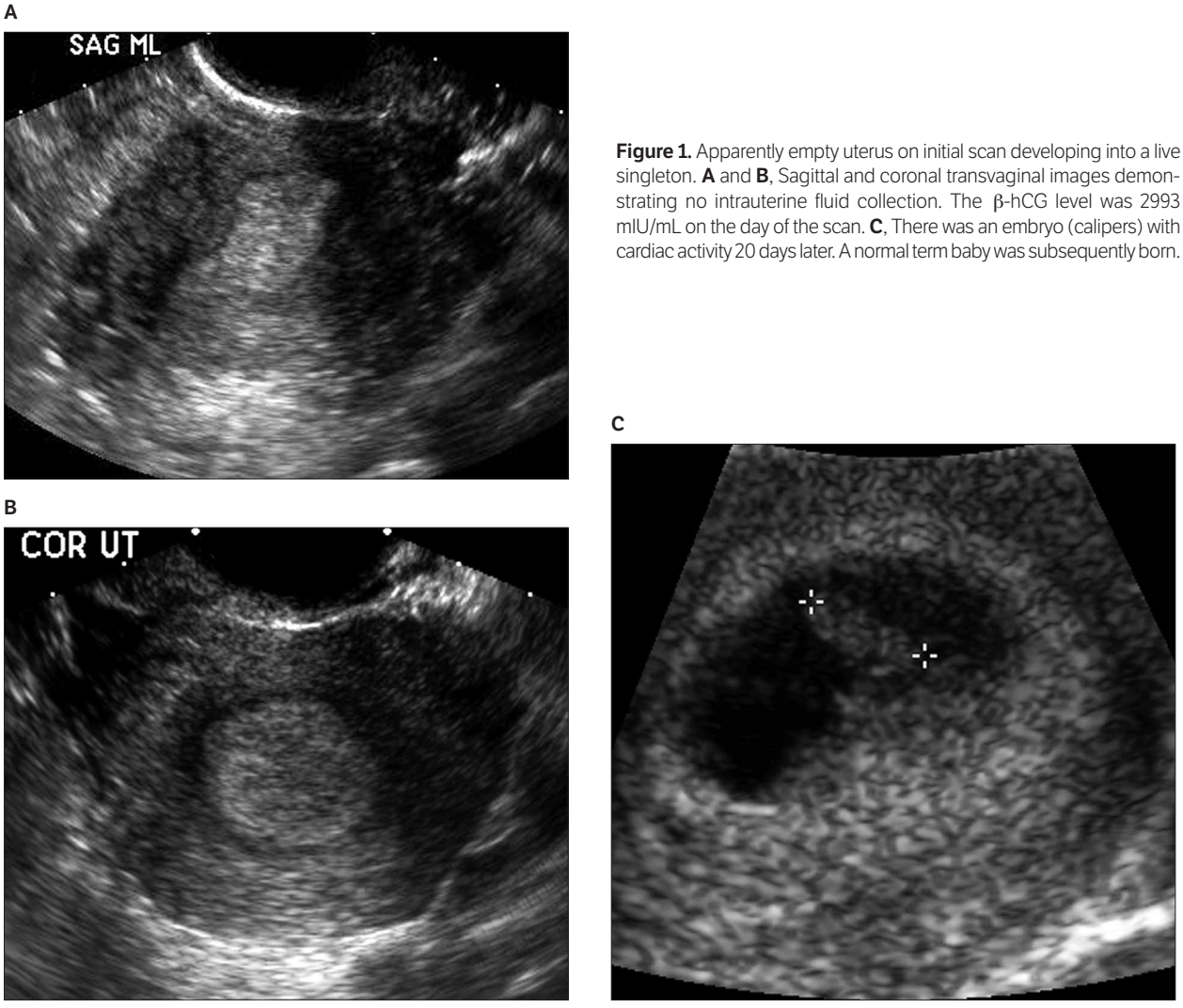

Figure 1. Apparently empty uterus on initial scan developing into a live singleton. **A** and **B**, Sagittal and coronal transvaginal images demonstrating no intrauterine fluid collection. The β-hCG level was 2993 mIU/mL on the day of the scan. **C**, There was an embryo (calipers) with cardiac activity 20 days later. A normal term baby was subsequently born.

Interventions such as dilatation and curettage and systemic methotrexate should be avoided in cases of suspected but unproven ectopic pregnancy if there is a chance that the woman has a normal intrauterine pregnancy. In view of this consideration, our results indicate that the hCG discriminatory level should not be used to determine the management of a hemodynamically stable patient with suspected ectopic pregnancy, if sonography demonstrates no findings of an intrauterine or ectopic pregnancy. Instead, follow-up sonography and serial hCG levels should be used before interventions for ectopic pregnancy are undertaken.

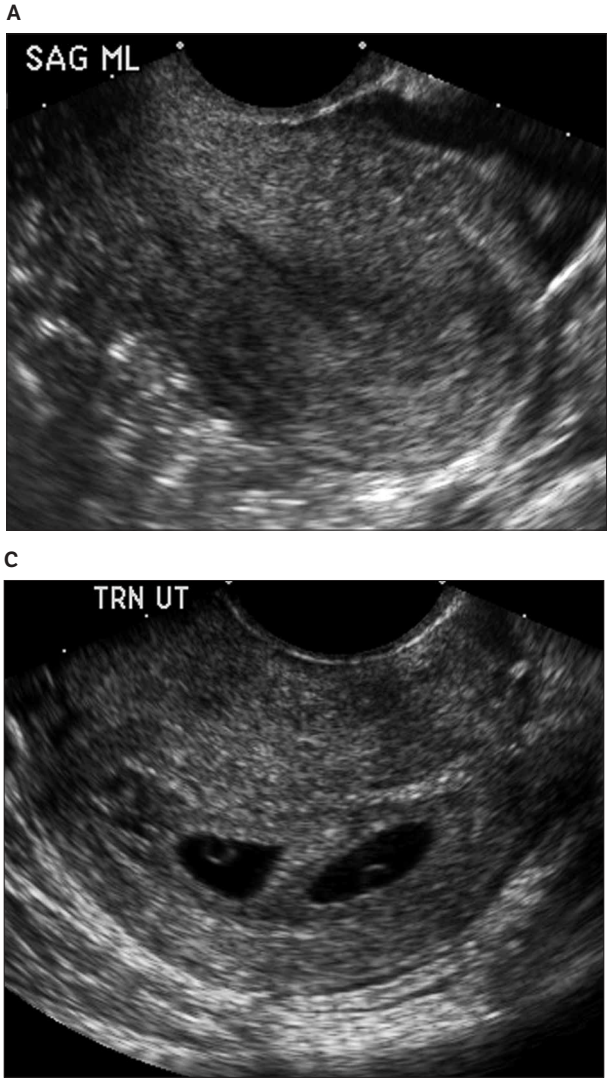

Figure 2. Apparently empty uterus on initial scan developing into a live twin gestation. **A** and **B**, Sagittal and coronal transvaginal images demonstrating no intrauterine fluid collection. The β-hCG level was 2217 mIU/mL on the day of the scan. **C**, Follow-up scan 6 days later demonstrated twins. Normal term twins were subsequently born.

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