Early Gestation:
Correlation of HCG Levels and Sonographic Identification

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Previous reports have indicated that an intrauterine gestational sac is not usually detected when the maternal serum human chorionic gonadotropin (HCG) is less than 6000 mIU/ml. In order to evaluate this observation, maternal serum HCG concentrations were correlated with sonographic uterine findings in 49 patients with normal early intrauterine pregnancies. Of 37 patients in whom a gestational sac was seen, simultaneous HCG levels were 1800 mIU/ml or more in 36 cases and 357 mIU/ml in one case. In 12 cases in which a gestational sac was not detected, the serum HCG levels were 1400 mIU/ml or less. Thirteen patients had HCG levels of less than 6000 mIU/ml. A linear relation was found between gestational sac size and the exponential rise of HCG levels in early pregnancy ($p < 0.001$). Of the 13 patients in whom HCG levels were less than 6000 mIU/ml, the gestational sac measured 10 mm or less in each case. Currently, a gestational sac is always seen when the HCG level is greater than 1800 mIU/ml. Comparison of serum HCG levels with sonographic detection of the gestational sac seems to be a useful method of evaluating early pregnancy.

Pelvic sonography and maternal serum pregnancy testing are commonly used to diagnose and evaluate patients in early pregnancy [1–6]. Accurate assessment of patients with early pregnancies is important, in order to distinguish symptomatic patients with normal intrauterine pregnancies from those with abnormal intrauterine or ectopic pregnancies [7–10]. While demonstrating a living intrauterine embryo by sonography is the most certain evidence of an intrauterine pregnancy, this is not usually possible until about 7 menstrual weeks [1, 2]. Recent investigations have aimed at earlier identification of a normal intrauterine pregnancy, before sonographic depiction of the embryo [9–12]. Demonstration of a double decidual sac finding allows confident identification of an intrauterine pregnancy (about 2 weeks earlier than detecting an embryo) and permits a true gestational sac to be distinguished from a pseudogestational sac, which is found in 10%–20% of patients with ectopic pregnancy [9, 10]. This finding does not, however, discriminate between normal and abnormal intrauterine pregnancies [9, 13].

Using a different approach, Kadar et al. [12, 13] correlated the sonographic appearance of the uterus with simultaneous quantitative human chorionic gonadotropin (HCG) concentrations in an effort to distinguish patients with normal pregnancies from those with abnormal intrauterine and ectopic pregnancies. They reported that an intrauterine gestational sac could first be detected by sonography when the serum HCG level reached a "discriminatory zone," which was found to be 6000–6500 mIU/ml. They found that failure to identify a gestational sac when the HCG level was above the discriminatory zone was highly suspicious for ectopic pregnancy. They further concluded that a normal gestational sac was rarely observed when the HCG concentration was less than the discriminatory zone, and that such a finding most likely represented an abnormal pregnancy or a pseudogestational sac of ectopic pregnancy [12]. Other reports suggest that a gestational sac may normally be detected at lower HCG concentrations [9, 14]. We report our recent experience correlating sonographic findings with quantitative HCG levels,

Received September 28, 1984; accepted after revision December 6, 1984.

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AJR 144:951–954, May 1985
0361–803X/85/1445–0951

showing that small intrauterine gestational sacs can be detected at HCG levels significantly lower than those reported by Kadar et al. [12, 13].

Materials and Methods

During a 2-year period (1982–1984), 49 patients from two hospitals with normal early intrauterine pregnancies had quantitative HCG determinations performed within 48 hr of sonography. All but two patients were referred for evaluation of possible ectopic pregnancy. The scans were performed on a variety of commercially available real-time and static scanners, using either 3.5- or 5.0-MHz transducers. In each case, a careful search was made for an intrauterine gestational sac, which, if found, was measured in three dimensions. The measurements were obtained from the inner sac wall, omitting the surrounding decidual reaction, to calculate a mean gestational sac diameter. The gestational sac was also examined for evidence of a double decidual sac finding, as well as for evidence of a living embryo. When more than one sonogram and HCG value were available on an individual patient, only the initial information was used for data analysis.

Serum HCG concentrations were determined by radioimmunoassay, using a commercially available kit (Clinetics, Tustin, CA) or an assay developed by the University of California, San Francisco laboratory. Both assays had less than 1% cross-reactivity with luteinizing hormone (LH) and used antibodies generated against the beta subunit of HCG. After either a 90 min or overnight incubation at room temperature, antibody-bound and free HCG-^{125}I were separated by a double antibody–polyethylene glycol procedure. The sensitivity of these assays was 5 mIU/ml. Both the intra- and interassay coefficients of variation were less than 10%. The assays were calibrated against the Second International Standard for Chorionic Gonadotrophin and reported as milliinternational units of HCG per milliliter of serum (mIU/ml). HCG concentrations were routinely reported to a maximum of 10,000 mIU/ml, and above this level by request.

Serum HCG levels were obtained on the same day as the sonogram in all but eight cases. In three patients, a single HCG determination was obtained within 1 day of the sonogram, while in five cases, it was obtained within 2 days of the sonogram. Four of these patients had serial (at least two) HCG levels available, so the HCG level on the day of sonography was easily interpolated. For the remaining patients, a doubling time of 48 hr was assumed. This assumption was considered valid on the basis of previously published information [5, 15, 16] as well as our own data obtained from more than 30 patients with normal early intrauterine pregnancies in whom serial HCG levels were performed.

Clinical follow-up and serum HCG levels were obtained from review of medical and laboratory records. Only those patients with normal gestations were included in the study group; all patients with ectopic pregnancy or abnormal gestational outcomes were excluded. Of the 49 patients, 43 had a normal outcome on the basis of either subsequent sonograms that demonstrated a living fetus (35 patients) or clinical follow-up (eight). In the six remaining cases, a single sonogram was followed by a therapeutic abortion. Nondegenerating chorionic villi in the pathologic material was supportive evidence for a normal gestation in these cases.

TABLE 1: **Detection of Gestational Sac by Sonography Correlated with Quantitative HCG Level in 49 Patients with Normal Intrauterine Pregnancies**

Quantitative HCG Level (mIU/ml)	No Sac	Gestational Sac	Gestational Sac and Embryo
≤1800	12	1	0
1800–6000	0	12	0
6000–10,000	0	2	0
>10,000	0	9	13

Results

Correlation of sonographic detection of the gestational sac with quantitative HCG levels is presented in table 1. Of the 49 patients in this study, a gestational sac was sonographically visible in 37 cases (13 of whom also had a visible embryo). In the 12 patients without visible evidence of a gestational sac, the HCG levels were 1400 mIU/ml or less. Of the 37 patients with a detectable gestational sac, 36 (97.3%) had HCG levels of 1800 mIU/ml or higher. Furthermore, in every case in which the HCG level was greater than 1800 mIU/ml, a gestational sac was observed by sonography. Of 24 patients with a visible gestation sac but no visible embryo, 13 (54.2%) had HCG values of less than 6000 mIU/ml (fig. 1). One patient with a HCG level of 357 mIU/ml demonstrated a very small (3–4 mm) gestational sac observed at 5.0 menstrual weeks. Serial HCG levels obtained on this patient exhibited a normal exponential rise, and a subsequent sonogram demonstrated a living embryo.

Correlation of the gestational sac size with quantitative HCG levels is presented in figure 2. Mean gestational sac

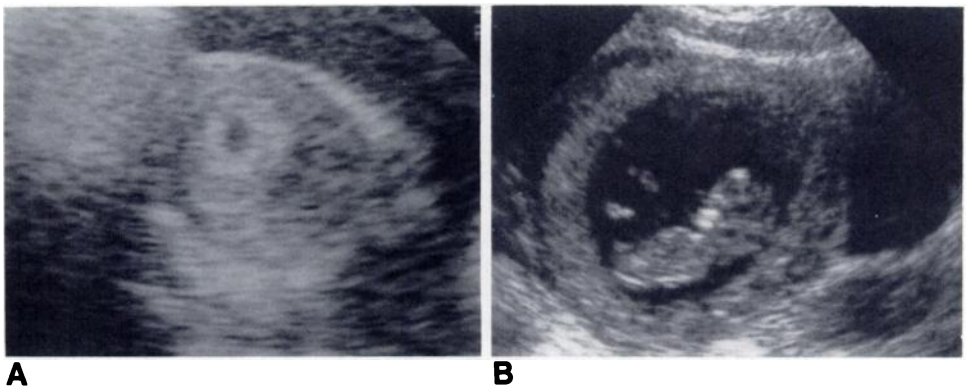

Fig. 1.—**A**, Transverse real-time sonogram. Intrauterine sac measures 10 mm in mean sac diameter. Maternal serum HCG level obtained same day was 3647 mIU/ml. Presence of double decidual sac, comprising two concentric echogenic rings, confirmed this sac to represent true gestational sac. **B**, 6 weeks later. Living fetus is shown.

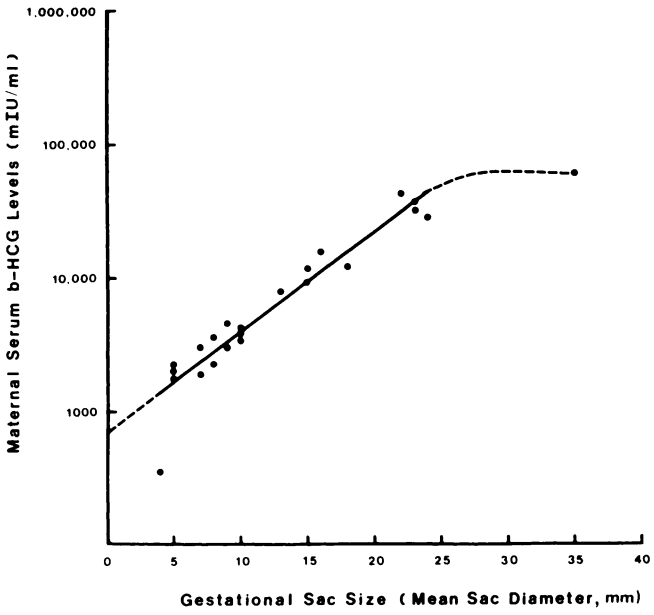

Fig. 2.—Comparison of maternal serum HCG levels with gestational sac size shows linear relation during early pregnancy. Regression line (solid line) is shown ($p < 0.001$). In later pregnancy, HCG levels decline while gestational sac continues to grow.

diameters ranged from 4 mm to 4 cm, associated with HCG levels of 357–61,000 mIU/ml.

Of 24 patients in whom a gestational sac but no embryo was detected by sonography, 23 had gestational sacs 4–18 mm in diameter; the HCG levels in these patients were 357–15,000 mIU/ml. The remaining case demonstrated a 24-mm gestational sac, associated with an HCG level of 27,000 mIU/ml; a subsequent therapeutic abortion yielded fetal parts. A subgroup of 13 of these 24 patients had HCG levels under 6000 mIU/ml (range, 357–4600 mIU/ml); the mean gestational sac diameter measured 10 mm or less in this subgroup (range, 4–10 mm). An HCG level of 6000 mIU/ml corresponds approximately to a sac diameter of 12 mm (fig. 2).

Regression analysis (fig. 2) demonstrates a linear relation of mean gestational sac size with the log of serum HCG concentrations in early pregnancy. This relation was highly significant ($p < 0.001$) below HCG levels of 43,000 mIU/ml. At higher HCG concentrations, this relation falls off as HCG levels plateau, while the gestational sac continues to grow.

The double decidual sac sign was definitely identified in 21 (87.5%) of 24 patients in whom a gestational sac without a visible embryo was detected. A double decidual sac was not definitely identified in three gestational sacs measuring 4, 7, and 8 mm in diameter.

Discussion

Recent advances in real-time sonography and the use of maternal serum pregnancy testing now permit reliable identification of very early intrauterine pregnancies before sonographic depiction of the living embryo. Such efforts have been primarily stimulated by examining patients with suspected ectopic pregnancy, since confirmation of an intrauterine pregnancy places a patient at low risk for harboring an ectopic gestation [7, 8]. Although a gestational sac may first be observed by sonography at 5–6 menstrual weeks, confusion with the "pseudogestational sac" of ectopic pregnancy has led authorities to rely on detection of a living embryo (after 7 menstrual weeks) for confirmation of an intrauterine pregnancy [1–4, 8]. Use of the recently described double decidual sac finding can now distinguish a true gestational sac from a pseudogestational sac, allowing a confident diagnosis of intrauterine pregnancy 10–14 days earlier than detection of an embryo [9, 10]. However, a double decidual sac may occasionally be difficult to discern in small gestational sacs.

Highly sensitive radioimmunoassays can detect maternal serum HCG up to 3 weeks before sonographic demonstration of an embryo [15, 17]. A single HCG level, however, does not discriminate intrauterine from extrauterine gestations. Serial quantitative HCG analysis can distinguish most patients with normal intrauterine pregnancies from those with abnormal and ectopic pregnancies, but this requires a minimum of 48 hr to complete [16].

Recently Kadar et al. [12, 13] introduced another method of evaluating early pregnancy by correlating sonographic findings of the uterus with simultaneous quantitative HCG levels. They found that a gestational sac is not normally detected at HCG levels below a discriminatory zone of 6000–6500 mIU/ml. The results of our study indicate that an early gestational sac is normally observed at substantially lower HCG levels than reported by Kadar et al. [12, 13]. However, the temporal difference is only slight. Because HCG levels rise exponentially, doubling every 2–3 days, an HCG level of 6000 mIU/ml is reached only 3–4 days later than a level of 2000 mIU/ml. From an imaging perspective, this is the difference between consistent resolution of a 7-mm gestational sac instead of a 12-mm gestational sac (fig. 2).

Our data confirm a linear relation between gestational sac size and the exponential rise of HCG levels in early gestation [18]. All 13 gestational sacs observed at HCG levels less than 6000 mIU/ml were less than 12 mm in mean gestational sac diameter. Although gestational sacs as small as 4 mm were detected, it is expected that such small sacs will be infrequently encountered in clinical practice. Gestational sacs small enough to produce low levels of HCG, but large enough to be resolved by sonography, lie in a narrow and generally asymptomatic time frame in pregnancy (5–6 weeks of amenorrhea).

Since quantitative HCG levels vary with gestational sac size, any apparent HCG discriminatory zone will most likely be a function of current or future sonographic technique and resolution. Given the progressive rise in HCG levels and normal growth of the gestational sac, it is reasonable to expect that at any given time in the technical advancement of sonographic equipment, there will exist an HCG level above which the gestational sac is always visible. Currently, at our institution, a gestational sac is always seen at HCG levels greater than 1800 mIU/ml. Whether this HCG threshold is shared by other investigators will obviously depend on sonographic technique and instrumentation. Methods of HCG de-

termination are less likely to produce a difference, since recent evidence suggests that there is little individual variation in quantitative HCG levels correlated with gestational age [11].

The relation of HCG levels to mean gestational sac size (fig. 2) is remarkably similar to the correlation of quantitative HCG levels with menstrual age [5, 11]. This similarity is not unexpected, since gestational sac size has previously been shown to grow at a constant rate with menstrual age. While it was not the purpose of this study to reexamine the relation between gestational sac size and menstrual age, our experience indicates that the mean gestational sac diameter increases about 1–1.5 mm per day for the first 50–60 days of pregnancy (menstrual age in days = mean sac diameter + 30). This experience is consistent with previous reports, correlating menstrual age with mean gestational sac diameter [18, 19] as well as by recalculation of data reported by Robinson [20] correlating gestational sac volumes with menstrual age. While gestational sac volumes are a more accurate measure of gestational sac size, the mean sac diameter is more conveniently measured and increases in a linear fashion compared with menstrual age, unlike the exponential rise of gestational sac volumes [20, 21]. Another important ancillary piece of information was gleaned during the recording of data from this study. A double decidual sac sign could be definitely identified in 87.5% of patients in whom a gestation sac, but no visible embryo, was seen. Thus, this morphologic feature, while relatively subtle, is nonetheless readily detected.

In summary, comparison of serum HCG concentrations with the sonographic appearance of the uterus seems to be an excellent method of evaluating early pregnancy, before detection of an intrauterine embryo. Appropriate correlation of sac size with the HCG level is supportive evidence for normal gestational development, whereas neither method alone can confirm a normal intrauterine pregnancy. The "discriminatory zone" concept seems limited at low HCG values. However, failure to detect an intrauterine sac at higher HCG levels is useful for suggesting a differential diagnosis of ectopic pregnancy or recent spontaneous abortion.

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