


Time to Revisit the Human Chorionic Gonadotropin Discriminatory Level in the Management of Pregnancy of Unknown Location

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Objectives—The purpose of this study was to review the management and outcomes of all patients with pregnancy of unknown location who had serum human chorionic gonadotropin (hCG) levels greater than 1000 mIU/mL in our institution and to determine the likelihood of a subsequent normal intrauterine pregnancy at different hCG discriminatory levels.

Methods—A retrospective review was performed on all women admitted with the diagnosis of pregnancy of unknown location and an hCG level greater than 1000 mIU/mL over a 5-year period (July 2007 to June 2012). Patients were identified from a computerized hCG result database. The medical records, including sonographic findings, hCG levels, and outcomes, were reviewed.

Results—A total of 113 patients were identified. There were 23 viable intrauterine pregnancies (20.4%) and 22 visualized ectopic pregnancies (19.5%). The highest hCG level associated with a subsequent normal intrauterine pregnancy was 9083 mIU/mL in a patient with triplet pregnancy. Possible factors associated with nonvisualization of a normal intrauterine pregnancy included uterine fibroids, adenomyosis, endometrial polyps, and obesity. The negative laparoscopy rate was 48.8%.

Conclusions—Viable intrauterine pregnancy is possible in patients with pregnancy of unknown location and hCG levels above the generally accepted discriminatory zone, strict adherence to which can potentially disrupt a normal pregnancy. We support the need for judicious use of the hCG discriminatory level in hemodynamically stable patients with pregnancy of unknown location, and the decision to intervene should not be based solely on a single hCG level.

Key Words—discriminatory level; ectopic pregnancy; gynecologic ultrasound; human chorionic gonadotropin level; pregnancy of unknown location

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Abbreviations

hCG, human chorionic gonadotropin

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Pregnancy of unknown location refers to a condition in which a woman has a positive pregnancy test result but no evidence of an intrauterine or extrauterine pregnancy on transvaginal sonography.¹ Follow-up of the woman is warranted until a final diagnosis is achieved. The reported incidence of pregnancy of unknown location in women attending early pregnancy assessment centers varies from 7% to 30%,² a higher incidence being associated with poor-quality sonography, inexperienced sonographers, ovarian or uterine disease causing poor visualization of the intrauterine cavity or adnexa, and other potential factors such as obesity and the presence of an intrauterine device. A consensus statement published by the International Society of Ultrasound in Obstetrics and Gynecology in 2006 suggested that the incidence of pregnancy of unknown location should be less than 15%.³

Over the years, the human chorionic gonadotropin (hCG) discriminatory level, the maternal serum hCG level above which a gestational sac should consistently be visible on transvaginal sonography, has been used to aid in the management of women with pregnancy of unknown location. The concept of the hCG discriminatory level was first reported in 1981 by Kadar et al,⁴ who showed that all intrauterine pregnancies in their study were visible on transabdominal sonography at an hCG level greater than 6500 mIU/mL. With improvement in the resolution of ultrasound imaging and the use of transvaginal sonography, the discriminatory level has been set progressively lower to 1000 to 2000 mIU/mL.^{5,6} Ectopic pregnancy is a cause of concern in the management of a woman with pregnancy of unknown location, which has serious consequences if the diagnosis is missed or delayed. Therefore, to rule out ectopic pregnancy, diagnostic laparoscopy is often considered if transvaginal sonography shows no evidence of an intrauterine pregnancy in a woman with serum hCG above the discriminatory level.

Of equal importance is the potential interruption of a normal intrauterine pregnancy due to unnecessary intervention in a woman with pregnancy of unknown location. Studies have demonstrated that most women with pregnancy of unknown location (80%–93%) in fact do not have an ectopic pregnancy.² A recent publication by Doubilet and Benson⁷ also reported a series of 9 normal intrauterine pregnancies subsequently documented in a group of woman who had hCG levels greater than 2000 mIU/mL, with no evidence of intrauterine gestation on initial transvaginal sonography. As women present earlier to medical facilities with only mild symptoms, and as diagnostic laparoscopy is not without risks, this diagnostic dilemma questions the need for intervention in asymptomatic patients with pregnancy of unknown location.

The objective of this study was to review the management and outcomes of all patients with pregnancy of unknown location who had serum hCG levels greater than 1000 mIU/mL in our institution and to determine the likelihood of a subsequent normal intrauterine pregnancy at different hCG discriminatory levels.

Materials and Methods

The study was conducted at the Department of Obstetrics and Gynecology, Queen Mary Hospital, a teaching hospital affiliated with the University of Hong Kong. Our institution has approximately 7800 gynecologic admissions per year and a dedicated early pregnancy assessment unit with more than 1700 consultations per year. Ethics approval

was obtained from the Hong Kong University Hospital Authority/Hong Kong West Cluster Institutional Review Board.

The study was a retrospective chart review performed over a 5-year period between July 2007 and June 2012. The standard protocol for patients attending the early pregnancy assessment unit or admitted to the gynecology ward with vaginal bleeding or abdominal pain in the first trimester was transabdominal followed by transvaginal sonography. Scans were performed by radiologists, with the exception of those who were pregnant as a result of assisted reproductive technology at the unit, the scans of whom were performed by reproductive medicine specialists. Serum hCG was taken in selected cases, including patients with pregnancy of unknown location, defined by the absence of an intrauterine or extrauterine pregnancy on transvaginal sonography or a visualized ectopic pregnancy, to aid management. Patients with pregnancy of unknown location and hCG levels greater than 1000 mIU/mL taken within 12 hours of sonography were identified from the hospital hCG database. Both assisted and unassisted pregnancies were included in the analysis. Those with hCG levels less than 1000 mIU/mL, an interval of more than 12 hours between blood taking for hCG testing and transvaginal sonography, hemodynamic instability at presentation, previous sonographic documentation of an intrauterine gestation, heavy vaginal bleeding, and a history of passage of a tissue mass before transvaginal sonography were excluded.

The hCG discriminatory level in our institution was 1000 mIU/mL, which was readjusted to 1500 mIU/mL in June 2011. Diagnostic laparoscopy was considered to rule out ectopic pregnancy when transvaginal sonography did not show any evidence of an intrauterine or extrauterine pregnancy and the hCG was above the discriminatory level, and any visualized ectopic pregnancy was treated accordingly during the operation. Serum hCG monitoring over 48 hours was allowed in selected cases if the patient had minimal symptoms and decided not to have laparoscopy. Transvaginal sonography was repeated when the hCG level showed a rise of greater than 53%. Laparoscopy was advised if there was a suboptimal rise in the hCG level, a visualized ectopic pregnancy on repeated transvaginal sonography, or development of symptoms or signs of hemoperitoneum. Medical therapy could also be considered at the discretion of the gynecologist. The hCG levels reported in our laboratory were equivalent to World Health Organization Third International Standard 75/537.

Patient records were reviewed, and information regarding the hCG levels, transvaginal sonographic findings, treatment, and outcomes was analyzed. Pregnancy

outcomes were categorized as visualized ectopic pregnancy, visualized intrauterine pregnancy, spontaneously resolved pregnancy of unknown location, and treated persistent pregnancy of unknown location, based on a consensus statement published in 2011 entitled “Pregnancy of Unknown Location: A Consensus Statement of Nomenclature, Definitions, and Outcome.”¹ A visualized ectopic pregnancy is a confirmed ectopic pregnancy identified by transvaginal sonography or at the time of surgery. A visualized intrauterine pregnancy is a confirmed intrauterine pregnancy identified by a transvaginal scan and is further subdivided into a viable intrauterine pregnancy, an intrauterine pregnancy of uncertain viability, and a nonviable intrauterine gestation. A spontaneously resolved pregnancy of unknown location refers a pregnancy of unknown location that has spontaneous resolution of serum hCG to undetectable levels without intervention. A treated persistent pregnancy of unknown location refers to a pregnancy with failed localization of the pregnancy on follow-up that is treated medically without confirmation of the location of the gestation.

Results

A total of 113 patients with pregnancy of unknown location and hCG levels greater than 1000 mIU/mL were identified over the study period. Table 1 shows the pregnancy outcomes with respect to different hCG levels. The hCG levels ranged from 1055 to 40,869 mIU/mL (median, 2411 mIU/mL). On subsequent follow-ups, 23 patients (20.4%) were confirmed to have viable intrauterine pregnancies on transvaginal sonography (Table 2). Of the 23 patients, 11 (47.8%) had given birth to neonates; 6 (26.1%) had terminations of pregnancy; 3 (13.0%) had

spontaneous miscarriages; and 3 (13.0%) had not had subsequent follow-up in our institution. For those patients who had given birth to neonates, 9 (81.8%) had uneventful term deliveries, and 2 (18.2%) had preterm deliveries, with both delivered at 32 weeks (1 for intrauterine growth restriction and 1 for a twin pregnancy with preterm prelabor rupture of membranes). The highest hCG level in those patients who had subsequent normal pregnancies was 9083 mIU/mL, which occurred in a patient with a trichorionic triamniotic triplet pregnancy conceived by in vitro fertilization. Fetal reduction was performed at 16 weeks to a dichorionic diamniotic twin pregnancy, and the neonates were delivered at 32 weeks after preterm prelabor rupture of membranes (patient 22 in Table 2). Identifiable factors that might have been associated with nonvisualization of an early viable intrauterine pregnancy included the presence of uterine fibroids, causing distortion or poor visualization of the endometrial cavity ($n = 2$; patients 1 and 20), adenomyosis ($n = 1$; patient 21), an endometrial polyp ($n = 1$; patient 5) and obesity ($n = 1$; patient 16, with a body mass index of 34.7 kg/m²).

Laparoscopies were performed in 43 patients, of which 21 (48.8%) had negative findings, and 22 (51.2%) confirmed ectopic pregnancies; all had surgical treatment performed in the same setting. Table 3 summarizes the hCG ranges, indications for laparoscopy, and pregnancy outcomes in patients who had negative laparoscopic findings and those who had visualized ectopic pregnancies at laparoscopy. One patient (with an hCG level of 1302 mIU/mL; patient 5 in Table 2) had serosal bowel injury during laparoscopy, which required laparotomy for repair. Laparoscopy was performed in 4 of the 23 patients who subsequently had normal intrauterine pregnancies, and all had negative findings.

Table 1. Pregnancy Outcomes With Respect to Different hCG Levels

hCG Range, mIU/mL	Visualized Ectopic Pregnancy	Visualized Intrauterine Pregnancy (Viable)	Visualized Intrauterine Pregnancy (Viability Uncertain, Nonviable, or Histologic)	Other ^a	Total
1000–2000	7	11	5	21	44
2000–3000	4	7	5	12	28
3000–4000	0	1	2	9	12
4000–5000	1	0	1	2	4
5000–6000	4	1	0	2	7
6000–7000	1	0	0	0	1
7000–8000	0	0	1	1	2
8000–9000	1	1	2	0	4
>9000	4	2	3	2	11
Total	22	23	19	49	113

^aIncludes resolved pregnancy of unknown location ($n = 45$), treated pregnancy of unknown location ($n = 2$), and molar pregnancy ($n = 2$).

Of the 22 patients with visualized ectopic pregnancies, all of them were treated surgically. Their hCG levels ranged from 1155 to 21,770 mIU/mL. Twenty patients (90.1%) had tubal ectopic pregnancies; 1 (4.5%) had a stump pregnancy (ectopic pregnancy at the stump of a previously removed tube); and 1 (4.5%) had an ovarian pregnancy. Five of 22 patients (22.7%) had laparoscopy immediately on diagnosis of pregnancy of unknown location. For the other patients (77.3%), the indications for laparoscopy included development of peritoneal signs, a suboptimal rise in the hCG level, and visualization of ectopic gestations on repeated transvaginal sonography. Five patients had ruptured ectopic pregnancies, 3 of whom had hCG levels less than 2000 mIU/mL at presentation, and 2 of whom had a ruptured tubal stump and an ovarian pregnancy with hCG levels of 8156 and 10064 mIU/mL, respectively.

Discussion

Transvaginal sonography and serum hCG measurements are paramount in the management of patients with suspected ectopic pregnancies. However, there is still no consensus as to the most optimal strategy in evaluating these patients. One limitation is the heterogeneity of inclusion criteria and terminology used in different studies.⁸ Therefore, there is a need for standardized definitions of populations and outcomes to allow objective comparisons of different studies for devising the most optimal care for women with pregnancy of unknown location. Based on a review of the literature and a series of collaborative international meetings, a consensus statement entitled “Pregnancy of Unknown Location: A Consensus Statement of Nomenclature, Definitions, and Outcome”¹ was published, with definitions of the population, target disease, and final outcome, from which the terminology in our study was derived.

Table 2. Patients With Viable Intrauterine Pregnancies

Patient	Initial hCG, mIU/mL	Possible Factors Associated With Nonvisualization of Intrauterine Pregnancy	Management	Outcome
1	1067	Uterine fibroids	Conservative	Miscarriage
2	1195	None	Conservative	Spontaneous vaginal delivery at term
3	1198	None	Conservative	2nd-trimester medical therapeutic abortion
4	1214	None	Conservative	Spontaneous vaginal delivery at term
5	1302	Endometrial polyp	Laparoscopy (bowel injury)	1st-trimester surgical therapeutic abortion
6	1348	None	Conservative	Last seen at 32 wk, with uneventful pregnancy
7	1468	None	Conservative	1st-trimester surgical therapeutic abortion
8	1526	None	Conservative	Spontaneous vaginal delivery at term
9	1601	None	Conservative	Spontaneous vaginal delivery at term
10	1766	None	Conservative	1st-trimester surgical therapeutic abortion
11	1938	None	Conservative	Spontaneous vaginal delivery at term
12	2131	None	Conservative	Miscarriage
13	2227	None	Conservative	1st-trimester surgical therapeutic abortion
14	2245	None	Conservative	Last seen at 35 wk, with uneventful pregnancy
15	2466	None	Laparoscopy	Vacuum extraction at term
16	2489	Obesity	Conservative	Spontaneous vaginal delivery at term
17	2756	None	Laparoscopy	1st-trimester medical therapeutic abortion
18	2943	None	Conservative	Cesarean delivery at term
19	3488	None	Conservative	Spontaneous vaginal delivery at term
20	5583	Uterine fibroids	Conservative	Last seen at 37 wk, with uneventful pregnancy
21	8420	Adenomyosis	Conservative	Cesarean delivery at 32 wk ^a
22	9083	None	Conservative	Caesarean delivery at 32 wk ^b
23	9497	None	Laparoscopy	Miscarriage

^aSevere intrauterine growth restriction and nonreassuring cardiotocographic findings.

^bTrichorionic triamniotic triplet pregnancy, fetal reduction to dichorionic diamniotic twin pregnancy, and preterm prelabor rupture of membranes.

Although for many decades, we have been using the hCG discriminatory level in the evaluation of patients with suspected ectopic pregnancies, its value in the current treatment of patients with pregnancy of unknown location has been called into question. A recent systematic review suggested that a single serum hCG level had poor performance in diagnosing ectopic pregnancies in women with pregnancy of unknown location.⁸ In a study of more than 5000 women attending an early pregnancy assessment unit in the United Kingdom, Kirk et al⁹ demonstrated that almost three-quarters of tubal ectopic pregnancies could be visualized on the initial transvaginal sonography, and the remaining cases of ectopic pregnancies could be visualized on subsequent transvaginal sonography, with overall sensitivity of 98.3%. With improvement in ultrasound technologies, the current trend in the diagnosis of ectopic pregnancies is mostly based on a positive visualization of an ectopic pregnancy rather than the absence of an intrauterine pregnancy.¹⁰ Most women with pregnancy of unknown location may therefore represent failing pregnancies of unknown location, complete miscarriages, self-limiting forms of ectopic pregnancy, and early intrauterine pregnancies that do not need active intervention. Nevertheless, it should be noted that, on the basis of our study, 19.5% of patients with pregnancy of unknown location and an initial hCG level greater than 1000 mIU/mL (22 of 113) had ectopic pregnancies.

Our findings agree with those of Doubilet and Benson,⁷ which clearly show that a normal intrauterine pregnancy is possible with an hCG level above the usual cutoffs of 1000 to 2000 mIU/mL.^{5,6} The importance of this factor is obvious in that a normal gestation may potentially be disrupted if the discriminatory level is purely relied on to decide on treat-

ment intervention in patients with presumed ectopic pregnancies, namely diagnostic laparoscopy and possibly diagnostic curettage or methotrexate administration.

The ideal discriminatory level should cause no disruption of normal intrauterine pregnancies and yet be able to diagnose most if not all ectopic pregnancies with the least number of negative or unnecessary laparoscopies. On the basis of our study, an hCG cutoff of greater than 9500 mIU/mL will exclude all intrauterine pregnancies, but if this hCG level is taken as the “discriminatory level,” there will be a trade-off of potentially missing or delaying the diagnosis of 86.4% of ectopic pregnancies (19 of 22). In addition to uterine fibroids, adenomyosis, and multiple gestations, the presence of an intrauterine device and endometrial polyps are also possible factors that can be associated with nonvisualization of intrauterine pregnancies.¹¹ Whether obesity is also a factor for poor visualization requires further studies, although obesity has been shown to decrease the diagnostic accuracy of endometrial thickness measurement.¹² Considerable thought should be given to repeating transvaginal sonography or hCG measurements in hemodynamically stable patients, rather than proceeding with surgical intervention or medical therapy, no matter what the initial hCG level is.

In our study, the negative laparoscopy rate was 48.8%. We expect that the number of laparoscopies with negative findings would have been even higher if we had strictly adhered to our institutional protocol, in which laparoscopies are considered in all patients with pregnancy of unknown location whose hCG is above the discriminatory level (Figure 1). The rate of ectopic pregnancies (19.5%) in our study was compatible with the reported rates of 7% to 20%.² This high rate could possibly have been due to

Table 3. Summary of hCG Ranges, Indications for Laparoscopy, and Pregnancy Outcomes in Patients With Negative Laparoscopic Findings and Visualized Ectopic Pregnancies at Laparoscopy

Parameter	Negative Laparoscopy (n = 21)	Visualized Ectopic Pregnancy (n = 22)
hCG range, mIU/mL	1,201–40,869	1,154– 21,770
Median hCG, mIU/mL	2,638	3,746
Reason for laparoscopy		
Suboptimal rise in hCG	11	5
Developed symptoms of ectopic pregnancy during monitoring	1	2
According to departmental protocol (performed directly for pregnancy of unknown location when initial hCG was above discriminatory level ^a)	9	5
Rescan showed ectopic pregnancy	0	10
Outcome	Intrauterine pregnancy (14), spontaneously resolved pregnancy of unknown location (5), partial mole (2)	Tubal ectopic (20), stump ectopic (1), ovarian ectopic (1)

^aThe hCG discriminatory levels in our institution were 1000 and 1500 mIU/mL before and after June 2011, respectively.

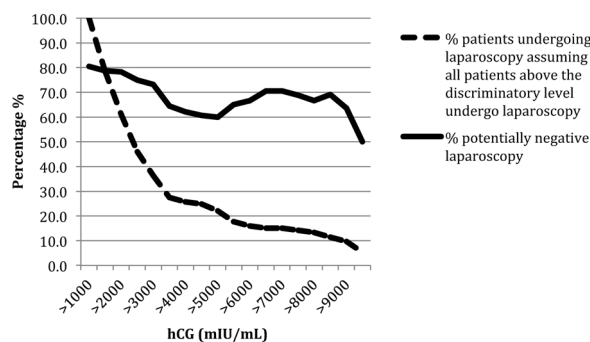


Figure 1. Hypothetical model using our data showing the percentage of patients undergoing laparoscopy assuming that all patients with hCG above the discriminatory level undergo laparoscopy and the percentage of potentially negative laparoscopies with respect to different hCG cutoffs.

the inclusion of high-risk groups such as patients who had undergone assisted reproduction and also to the fact that our center accepts referrals for patients with early pregnancy complications.

This study had the following limitations: (1) Because of its retrospective nature, some patients might have been misclassified or missed without inclusion in our series. (2) There was an interval of up to 12 hours between blood taking and transvaginal sonography. This interval was present for logistic reasons because patients might not have immediate access to transvaginal sonography at the time of admission and blood taking. However, we believe that the difference in the hCG levels over a maximum 12-hour interval should be less than 20% (based on the normal hCG rise of at least 35% in 48 hours¹³) and was unlikely to alter clinical management. We suggest that, in ideal clinical scenario, blood taking for hCG measurement and transvaginal sonography should be performed simultaneously. (3) There was a lack of standardization of the scanning protocol. In our study, only 5 of 23 patients were found to have an anatomic reason for nonvisualization of the gestational sac. Although most scans were performed by radiologists, some were performed by gynecologists, and the machine used or scanning approach may not have been uniform. (4) This study was unable to determine the likelihood of a normal intrauterine pregnancy in a woman with hCG above the discriminatory level and with nothing seen inside the uterus. We did not have the total number of scans or hCG measurements performed in the unit for the denominator and also did not have reference standard confirmatory tests to determine the ultimate pregnancy locations in most patients with pregnancy of unknown location that had spontaneously resolved. Furthermore, an institu-

tion that provides mostly acute gynecologic services will obviously have a different ratio from one that only provides low-risk care. Our goal was in fact not to determine a particular likelihood of a normal pregnancy in a general sense but to demonstrate that a normal pregnancy was possible in patients with pregnancy of unknown location and hCG levels above the commonly accepted discriminatory zone; thus, caution should be exercised when managing this group of patients.

In the current medicolegal environment, mismanaging early pregnancy complications can lead to potentially serious consequences. It is clear that a normal intrauterine pregnancy can present as pregnancy of unknown location above the usual hCG discriminatory level. Strict adherence to the discriminatory level can lead to unnecessary interventions, which are not without risks, and can inadvertently disrupt a viable developing intrauterine pregnancy. Our data suggest that the concept of an hCG discriminatory level in the management of pregnancy of unknown location is potentially dangerous. We support the need for judicious use of the hCG discriminatory level in hemodynamically stable patients with pregnancy of unknown location, and the decision to intervene should not be based solely on a single hCG level.

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