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Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location

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ABSTRACT

Objectives *Various serum human chorionic gonadotropin (hCG) discriminatory zones are currently used for evaluating the likelihood of an ectopic pregnancy in women classified as having a pregnancy of unknown location (PUL) following a transvaginal ultrasound examination. We evaluated the diagnostic accuracy of discriminatory zones for serum hCG levels of > 1000 IU/L, 1500 IU/L and 2000 IU/L for the detection of ectopic pregnancy in such women.*

Methods *This was a prospective observational study of women who were assessed in a specialized transvaginal scanning unit. All women with a PUL had serum hCG measured at presentation. Expectant management of PULs was adopted. These women were followed up with transvaginal ultrasound, monitoring of serum hormone levels and laparoscopy until a final diagnosis was established: a failing PUL, an intrauterine pregnancy (IUP), an ectopic pregnancy or a persisting PUL. The persisting PULs probably represented ectopic pregnancies which had been missed on ultrasound and these were incorporated into the ectopic pregnancy group. Three different discriminatory zones (1000 IU/L, 1500 IU/L and 2000 IU/L) were evaluated for predicting ectopic pregnancy in this PUL population.*

Results *A total of 5544 consecutive women presented to the early pregnancy unit between 25 June 2001 and 14 April 2003. Of these, 569 (10.3%) women were classified as having a PUL, 42 of which were lost to follow up. Of the 527 (9.5%) cases with PUL analyzed, there were 300 (56.9%) failing PULs, 181 (34.3%) IUPs and 46 (8.7%) ectopic pregnancies. Overall, 74.6% were symptomatic and 25.4% were asymptomatic (*$P = 8.825E{-}07$*). The sensitivity and specificity of an hCG level of > 1000 IU/L to detect ectopic pregnancy were 21.7% (10/46) and 87.3% (420/481), respectively; for an hCG level of > 1500 IU/L these values were 15.2% (7/46) and 93.4% (449/481), respectively, and for an hCG level of > 2000 IU/L they were 10.9% (5/46) and 95.2% (458/481), respectively.*

Conclusions *Varying the discriminatory zone does not significantly improve the detection of ectopic pregnancy in a PUL population. A single measurement of serum hCG is not only potentially falsely reassuring but also unhelpful in excluding the presence of an ectopic pregnancy.*

INTRODUCTION

Historically, the introduction of transabdominal ultrasound to gynecology changed and significantly improved the management of women with suspected ectopic pregnancy. The combination of a positive pregnancy test and the absence of an intrauterine gestational sac on transabdominal sonography became generally accepted as an indication for laparoscopy. However, the same sonographic observations are by no means specific and can also be seen in intrauterine pregnancies (IUPs) that are too early to visualize or in failing pregnancies/trophoblast in regression[1].

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The non-specific nature of failing to visualize an intrauterine sac on transabdominal ultrasound was well recognized by Kadar *et al.*[2,3]. In 1980, the discriminatory human chorionic gonadotropin (hCG) zone was introduced, defined as the level of serum hCG above which one should always visualize an intrauterine sac on ultrasound. Thus the likely diagnosis of an ectopic pregnancy could be made when an intrauterine sac was absent on transabdominal ultrasound examination and the serum hCG was above the discriminatory zone of 6500 IU/L[2–4]. The probability of an ectopic pregnancy in such circumstances exceeded 95%. With the advent of high-resolution transvaginal probes, the diagnosis of an IUP was possible earlier and the diagnosis of ectopic pregnancy became more accurate[5]. As a consequence, the level of the discriminatory zone was decreased[6–10].

In modern practice, when the location of a pregnancy cannot be confirmed as an IUP or an extrauterine pregnancy on the basis of a transvaginal scan, this is classified as a pregnancy of unknown location (PUL). We advocate a non-surgical 'wait and see' approach in such circumstances, which has been prospectively validated in many studies[1,8,11–14]. An understanding of the pattern of serum hCG behavior in early normal pregnancy[3] and the correlation between low serum progesterone levels and the spontaneous resolution of a pregnancy[9] are important concepts in the management of PULs.

Between 8% and 31% of women who present to an early pregnancy unit are classified as having a PUL[11–13]. This is a descriptive term rather than a pathological entity. The varying prevalence of PULs might be attributable to a sonographer's ability to visualize IUPs or extrauterine pregnancies. An inexperienced sonographer could overlook some early intrauterine gestational sacs or adnexal masses, which in turn would result in a higher prevalence of PUL for a given early pregnancy unit.

The concept of combining ultrasound with measurements of serum hCG using a discriminatory zone has been well described[6–10]. By correlating serum hCG values with the size of the intrauterine gestational sac, a value can be chosen that corresponds to the threshold above which an intrauterine gestational sac should be seen. If a sac cannot be seen above this threshold value then steps must be taken to determine whether the pregnancy is abnormal or ectopic. Consequently, various discriminatory zones are used as a marker for the likelihood of an ectopic pregnancy in a woman classified as having a PUL.

These levels are dependent upon the quality of the ultrasound equipment, the experience of the sonographer, prior knowledge of the woman's risks and symptoms and the presence of physical factors such as uterine fibroids and multiple pregnancies. Whenever sonographic skills are highly developed, the majority of PULs will not have an underlying ectopic pregnancy. The varying prevalence of diagnosed ectopic pregnancy in PUL populations, between 10.8% and 42.8%, reflects scanning capabilities of different units[1,12–15].

In this study, we evaluated discriminatory zones of serum hCG levels of >1000 IU/L, 1500 IU/L and 2000 IU/L for the detection of ectopic pregnancy in such women in an ultrasound based unit.

METHODS

We undertook a prospective observational study of all 5544 consecutive women attending the early pregnancy unit at St. George's Hospital, London, between 25 June 2001 and 14 April 2003 inclusive. This group of women was also analyzed to evaluate a single-visit strategy in the management of PULs, the results of which were published elsewhere[16]. All of the women underwent a transvaginal ultrasound examination with a 5-MHz probe (Aloka SSD 900, 2000 or 4000, Keymed Ltd, Southend, UK and Aloka Co. Ltd., Tokyo, Japan). In a woman with a positive urinary pregnancy test a PUL was defined on the basis of transvaginal sonography if there were no signs of an IUP, an extrauterine pregnancy, or retained products of conception. Peripheral blood was taken from these women at presentation to measure the levels of serum hCG (World Health Organization, Third International Reference 75/537) and progesterone (Roche Elecsys 2010 Progesterone II test, Roche Diagnostics, Lewes, UK) using automated electrochemiluminescence immunoassays (ECLIA). These levels were measured again 48 h later, according to the unit's protocol.

Exclusion criteria included any of the following: 1) visualization of any evidence of an intrauterine sac; 2) identification of an adnexal mass thought to be an ectopic pregnancy; 3) presence of heterogeneous, irregular tissues within the uterus thought to be an incomplete miscarriage; 4) women who were clinically unstable or had a hemoperitoneum according to the ultrasound examination.

All women classified with PULs were followed up with monitoring of serum hormone levels, transvaginal ultrasound and/or laparoscopy until a final clinical diagnosis was established. These included failing PULs (trophoblast in regression), IUPs, ectopic pregnancies and persisting PULs.

Women were classified as having a failing PUL when neither an IUP nor an extrauterine pregnancy was visualized on transvaginal ultrasound and the serum hCG level fell to <5 IU/L. The location of these failing PULs remained unknown and a proportion of these pregnancies were probably failing ectopic pregnancies, never visualized using transvaginal ultrasound.

Women were classified as having an IUP when a gestational sac was visualized within the endometrial cavity using transvaginal ultrasound, eccentrically placed and with a hyperechoic ring. These women were rescanned 2 weeks later to confirm viability.

An ectopic pregnancy was diagnosed based on the positive visualization of an adnexal mass on gray-scale transvaginal ultrasound, i.e. if one of the following was observed: 1) a heterogeneous mass or blob sign adjacent to the ovary which moved independently of this[17]; 2) a

mass with a hyperechoic ring around the gestational sac (referred to as the bagel sign)[17]; 3) a gestational sac with a fetal pole with or without cardiac activity[17]. The diagnosis was subsequently confirmed, in those treated surgically, at laparoscopy with histological confirmation of chorionic villi in the Fallopian tube.

Women were classified as having a persisting PUL when the serum hCG levels failed to decline, and the location of the pregnancy could not be identified using transvaginal ultrasound[18]. The serum hCG levels were low (< 500 IU/L) and had reached a plateau, at which point treatment with methotrexate was given and their serum hCG levels declined[18]. These probably represented sonographically missed ectopic pregnancies. As they behaved like ectopic pregnancies biochemically and in order to classify them according to the worst-case scenario, these were incorporated into the ectopic pregnancy group. The first four in this group underwent both uterine curettage and laparoscopy, which were negative.

The data recorded included presenting complaints and levels of serum hCG and progesterone at time of presentation. All results were reviewed and followed up by the same primary investigator (G.C.).

Various discriminatory zones (1000 IU/L, 1500 IU/L and 2000 IU/L) were tested on this PUL population in order to evaluate their ability to predict ectopic pregnancy.

Statistical analysis

The performance of each of the discriminatory zones was evaluated in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Statistical analyses were conducted with SAS (version 8.2 for Windows, SAS, Cary, NC, USA). For categorical variables, Fisher's exact tests were used to check their association between the groups. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Of the 5544 consecutive women who presented to the early pregnancy unit during the study period, 569 (10.3%) were classified as having a PUL and 42 of these were lost to follow up. We therefore analyzed 527 (9.5%) PULs and the final clinical outcomes were 300 (56.93%) failing PULs, 181 (34.35%) IUPs and 46 (8.73%) ectopic pregnancies; nine persisting PULs were included in the final ectopic pregnancy group.

Of the 500 for whom presenting complaints were available, 74.6% were symptomatic and 25.4% were asymptomatic (Table 1), a significant difference ($P =$ 8.825E–07). In the failing PUL group, 26% presented with no vaginal bleeding, 52% with vaginal bleeding and 22% with vaginal bleeding with clots. In the IUP group, 77% presented with no vaginal bleeding, 21% with vaginal bleeding and 2% with vaginal bleeding with clots. In the ectopic pregnancy group, 35% presented with no vaginal bleeding, 60% with vaginal bleeding and 5% with vaginal bleeding with clots. The relative proportions of women with or without vaginal bleeding in the three outcome groups were significantly different ($P = 5.768$E–29; Figure 1). In the failing PUL group, 59% presented with no lower abdominal pain and 41% with lower abdominal pain. In the IUP group, 48% presented with no lower abdominal pain and 52% with lower abdominal pain. In the ectopic pregnancy group, 62% presented with no lower abdominal pain and 38% with lower abdominal pain. The relative proportions of women with or without lower abdominal pain in the three outcome groups were also significantly different ($P = 0.0494$; Figure 2).

The mean serum hCG and progesterone levels at diagnosis were 561 IU/L and 34 nmol/L, respectively (Table 2).

The sensitivity, specificity, PPV and NPV of the three discriminatory zone serum hCG levels to detect ectopic pregnancy are given in Table 3.

Table 1 Asymptomatic vs. symptomatic for each outcome group ($n = 500$*; $P = 8.825$E–07)

Group	*Asymptomatic* (n (%))	*Symptomatic* (n (%))
Failing PULs	42 (15)	234 (85)
IUPs	65 (37)	112 (63)
Ectopic pregnancy	10 (27)	27 (73)
Total	117 (25.4)	373 (74.6)

*Of the original 527, there were 27 with missing presenting complaints. IUP, intrauterine pregnancy; PUL, pregnancy of unknown location.

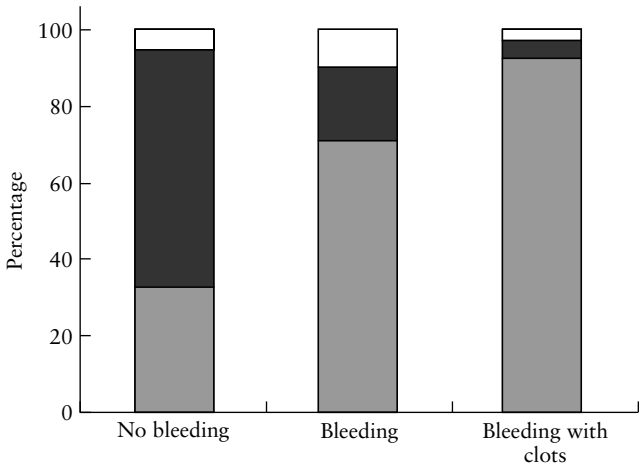

Figure 1 Relative proportion of cases with vaginal bleeding in the three outcome groups: (■) intrauterine pregnancies, (□) failing pregnancies and (□) ectopic pregnancies ($P = 5.768$E–29).

Table 2 Serum human chorionic gonadotropin (hCG) and progesterone levels at presentation

	n	*Median*	*Mean*	*Minimum*	*Maximum*	*SD*
hCG (IU/L)	527	272.00	561.12	6.00	9417.00	936.93
Progesterone (nmol/L)	527	15.00	33.5	1.00	191.00	36.64

Table 3 Sensitivities, specificities and positive and negative predictive values (PPV and NPV) for detection of ectopic pregnancy with varying discriminatory zones

Serum hCG	*True positive* (n)	*True negative* (n)	*False positive* (n)	*False negative* (n)	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
> 1000 IU/L	10	420	61	36	21.7	87.3	14.1	92.1
> 1500 IU/L	7	449	32	39	15.2	93.4	18.0	92.0
> 2000 IU/L	5	458	23	41	10.9	95.2	17.9	91.8

hCG, human chorionic gonadotropin.

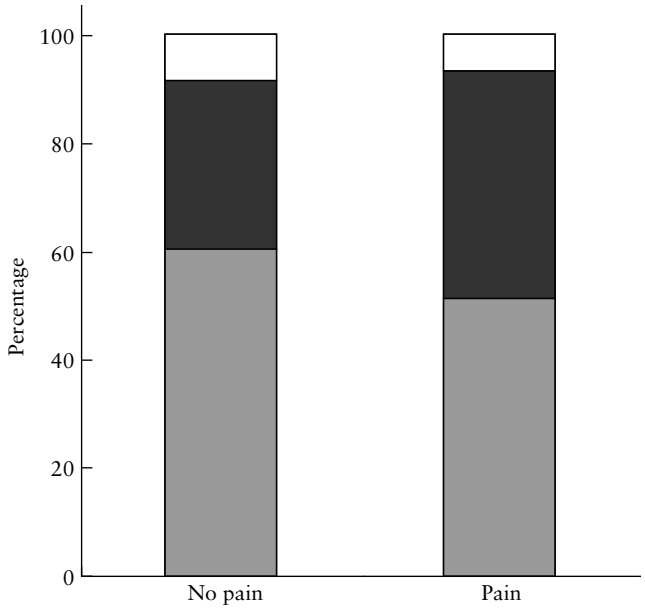

Figure 2 Relative proportion of cases with lower abdominal pain in the three outcome groups: (■) intrauterine pregnancies, (▩) failing pregnancies and (□) ectopic pregnancies ($P = 0.0494$).

DISCUSSION

This study prospectively evaluated the use of single levels of serum hCG to characterize the nature of PULs in women attending a specialized transvaginal scanning unit. The overall prevalence of ectopic pregnancies was 8.7%. This is significantly lower than in the published literature, and this almost certainly reflects a protocol based on the positive visualization of an adnexal mass using transvaginal ultrasound, rather than the absence of an intrauterine gestational sac. In our unit and others, 87–93% of ectopic pregnancies are diagnosed before surgery using transvaginal ultrasound alone[6,19,20]. It can be argued that the prevalence of ectopic pregnancy in a PUL population reflects the quality of scanning in a particular unit; this prevalence has been reported to be as high as 36–42.8%[1,15]. We believe that ectopic pregnancies are potentially missed in units where less emphasis is placed upon the use of gynecological ultrasound. This in turn results in more women being classified as having a PUL or having inconclusive scans, and in turn overinflates the prevalence of ectopic pregnancies in the PUL group. As the number of ectopic pregnancies in a PUL population increases, so too does the effectiveness of the discriminatory zone[1,8,15]. The sensitivity of the discriminatory zone for the detection of ectopic pregnancy in this study was much lower than that reported in some other studies[1,8,15]. We accept that the reproducibility of these results is dependent upon the sonographic skills of a unit; however, with adequate training in early pregnancy scanning and quality control, these results are achievable. Studies from highly specialized sonographic units have similar rates of ectopic pregnancy (between 10.8% and 14%) in PUL populations to those found in this study[12,13,21].

In a previous study from our unit based on the same population, serum progesterone in addition to serum hCG at presentation correctly classified 84% of non-ectopic pregnancies[17]. We believe that although the combination of the serum hCG and progesterone at the first visit provides additional information about the viability of the PUL, it does not help in locating the PUL.

It is important to be clear that the women in this study were thought to have a PUL and not an ectopic pregnancy at the time of their initial ultrasound scan. This cohort of patients is different from women who are diagnosed with an ectopic pregnancy based upon the initial positive visualization of an adnexal mass using transvaginal ultrasound[19]. We relied on ultrasound and not the routine use of uterine curettage to rule out an ectopic pregnancy in our PUL population. Although this approach does not confer 100% sensitivity, it is safe, non-invasive and associated with a low false-positive rate of 5.9%. The American Society for Reproductive Medicine advocates the use of uterine curettage to rule out an ectopic pregnancy if the serum hCG levels are > 2400 IU/L. If we had adopted this approach, we would have performed 21 uterine curettages: ten in the failing PUL group, seven in the IUP group and four in the ectopic pregnancy group. This would certainly have accurately classified the failing PULs as either IUPs or extrauterine pregnancies. However, such an approach would potentially have terminated two viable ongoing pregnancies in the IUP group and for this reason we do not advocate its use. It is true that we do not know the number of true ectopic pregnancies in the failing PUL group, but the fact that these pregnancies fail, combined with the potential to cause harm in the intrauterine group reinforces an expectant 'wait and see' approach.

The use of the discriminatory zone has been previously disputed[22,23]. According to Kadar *et al.*[22], the gestational age rather than the serum hCG level should be used in the diagnosis of ectopic pregnancy. We do not believe that gestational age is an important variable in the diagnosis

of ectopic pregnancy. In an earlier study in our unit, this variable was not significantly different in PUL outcome groups (failing PULs, IUPs and ectopic pregnancies)[24]. This finding is corroborated in a study by Mol *et al.*[25], in which the gestational age was not useful in the diagnosis of ectopic pregnancy. In another study disputing the use of the discriminatory zone, Mehta *et al.*[23] concluded that a serum hCG level of 2000 IU/L without ultrasound findings of an IUP was not diagnostic of an ectopic pregnancy. The findings in their retrospective study were based upon a cohort of women in which an ectopic pregnancy was suspected clinically. This is fundamentally different from the PUL population in our study, in which women were clinically stable and the vast majority were not thought to have an underlying ectopic pregnancy. Furthermore, the diagnosis of an ectopic pregnancy according to Mehta *et al.*[23] was based on an outdated approach, i.e. the absence of an IUP on ultrasound. In modern practice the diagnosis of an ectopic pregnancy should be based upon the positive visualization of an adnexal mass[19].

A criticism of this study is that it did not take into account the presenting complaints of the women when evaluating the different discriminatory zones. The use of probabilistic decision rules in the algorithms for the work-up of suspected ectopic pregnancy has been demonstrated to increase the diagnostic performance of such algorithms as compared to inflexible algorithms using rigid cut-off values[26]. The relative proportions of women with or without vaginal bleeding in the three outcome groups were statistically significantly different ($P = 5.768\text{E}{-29}$), as was the relative proportion with or without lower abdominal pain ($P = 0.0494$). Consequently, the diagnostic performance of the various discriminatory zones may well have been improved with the incorporation of these clinical factors.

Our data demonstrate that using a single value of serum hCG in a PUL population is of limited value. Many ectopic pregnancies in a PUL population have a relatively low serum hCG level, and so many clinicians may be falsely reassured about the likely location of the pregnancy. In contrast, a significant proportion of failing PULs and early IUPs in a PUL population have high serum hCG levels at presentation and, as is the case in the United States, may undergo unnecessary intervention in the form of uterine curettage. We contest that the majority of ectopic pregnancies should be diagnosed at the time of the initial visit using ultrasound alone[19]; serum hCG levels in this situation do not contribute to the diagnosis but assist in the management plan. When the situation is unclear and there is a PUL, it is the change in serum hCG over time that is important rather than any absolute initial serum value of hCG. Using an arbitrary discriminatory zone as a basis to manage these women is not recommended on the basis of this study.

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