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Do levels of serum cancer antigen 125 and creatine kinase predict the outcome in pregnancies of unknown location?

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BACKGROUND: The aim of this study was to evaluate the role of maternal serum cancer antigen 125 (CA 125) and creatine kinase (CK) levels in predicting the outcome of pregnancies of unknown location (PUL). METHODS: Prospective observational study. Women classified as PUL were recruited. Final outcome of each PUL was established: failing PUL, intrauterine pregnancy (IUP), ectopic pregnancy (EP) or persisting PUL. The persisting PUL group almost certainly represent ultrasonically missed EP and were included in EP group. Serum CK and CA 125 were measured at 0 and 48 h. The values at presentation and the change in levels after 2 days were used in the analysis. We incorporated the most significant of variables into a multinomial logistic regression model to predict all outcomes. The performance of this model was evaluated using receiver operating characteristic (ROC) curves. RESULTS: In all, 4698 consecutive women were scanned; 403 were classified as PUL, 27 were lost to follow-up. Of the 376 women eligible, 297 had complete data and therefore were recruited. Mean age and mean gestation were 30.0 years and 43.3 days respectively. Final outcomes: 153 failing PUL (51.5%), 116 IUP (39.1%) and 28 EP (9.4%). Mean serum CK levels at 0 and 48 h were 88.5 and 86.8 IU/l respectively. Mean serum CA 125 levels at 0 and 48 h were 43.8 and 40.1 kIU/l respectively. 81.1% of women had CK and CA 125 ratios (CK 48 h/CK 0 h, CA 125 48 h/CA125 0 h) between 0.7 and 1.3. CA 125 ratio was the only significant variable in the three outcome groups ($P < 0.0001$). Logistic regression analysis incorporating CA 125 ratio gave an area under ROC curve of 0.782 (SE = 0.041) for failing PUL, 0.768 (SE = 0.043) for IUP and 0.560 (SE = 0.078) for EP. This model was capable of distinguishing failing PUL from IUP, but was not able to detect EP. CONCLUSIONS: Absolute levels of serum CK and CA 125 at the defined times cannot be used to predict the outcome of PUL. Although the CA 125 ratio when incorporated into logistic regression model can distinguish failing PUL from IUP, its inability to detect the high risk PUL, i.e. the developing EP, renders it inappropriate for use in the clinical setting.

Key words: cancer antigen 125/creatine kinase/ectopic pregnancy/pregnancy of unknown location/transvaginal ultrasonography

Introduction

Cancer antigen 125 (CA 125) is an antigenic determinant on a high molecular weight glycoprotein recognized by a monoclonal antibody which was raised using an ovarian cancer cell line as an immunogen (Jacobs and Bast, 1989). Serum CA 125 levels peak during the first trimester of pregnancy, between the sixth and seventh weeks, and drop to non-pregnant values in the second and third trimester (Jacobs *et al.*, 1990; Check and Vetter, 1995). Elevated CA 125 levels in maternal serum originate from the decidual cells affected by chorionic invasion or placental separation (Kobayashi *et al.*, 1989).

Although there is evidence to suggest that serum CA 125 levels do not predict spontaneous miscarriage in the first trimester of pregnancy (Hornstein *et al.*, 1995), there is conflicting evidence regarding the use of CA 125 to differentiate between intrauterine pregnancies (IUP) and extrauterine pregnancies. Serum CA 125 levels have been reported to be significantly lower in ectopic pregnancies (EP) compared with IUP (Kobayashi *et al.*, 1993); however, in a larger, more recent study single serum measurements of CA 125 failed to discriminate between spontaneous miscarriage, EP or normal pregnancies (Schmidt *et al.*, 2001). Interestingly, serum CA 125 levels have been used to differentiate tubal abortion and viable EP (Predanic, 2000).

Creatine kinase (CK) is a key enzyme for energy metabolism of contraction and relaxation in both striated muscles (such as skeletal and cardiac) and smooth muscle. CK has been found in all smooth muscles studied to date including the fallopian tube (Clark, 1994). One theory is that damage to the fallopian tube in EP is sufficient to cause an increase in serum

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CK (Lavie *et al.*, 1993). Although some studies have demonstrated that maternal serum CK levels can be an important biochemical marker for the diagnosis of EP (Chandra and Jain, 1995; Duncan *et al.*, 1995), the general view is that maternal serum CK concentrations do not reliably predict EP (Korhonen *et al.*, 1996; Qasim *et al.*, 1996; Vandermolen and Borzelleca, 1996; Zorn *et al.*, 1997).

Pregnancies of unknown location (PUL) account for 8–31% of ultrasound scans performed in an early pregnancy setting (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999; Condous *et al.*, 2004a). In the current management of women with PUL, various serum hormones, including serum HCG and progesterone, are taken at defined times in order to facilitate a diagnosis. In a recent study, serum HCG and progesterone levels at defined times predicted the immediate viability of a PUL, but did not reliably predict its location (Condous *et al.*, 2004a).

To date, there are no published data on the use of serum CK and CA 125 taken at defined times to predict the outcome in women with a PUL. In this study, we assessed the role of maternal serum CA 125 and CK levels in such women.

Materials and methods

Data collection

This was a prospective observational study performed between March 4, 2002 and July 17, 2003. The local Ethics Committee granted ethical approval. During the study period, pregnant women presented to the Early Pregnancy Unit (EPU) at St George's Hospital, London. Transvaginal sonography (TVS) was used to detect morphological evidence of an IUP or EP. If the pregnancy could not be located, the woman was classified as having a PUL. Peripheral blood was taken to measure the levels of serum HCG (HCG, World Health Organisation, Third International Reference 75/537) and progesterone (Roche Elecsys 2010 Progesterone II test) using automated electrochemiluminescence immunoassays. These levels were measured 48 h later, according to our Unit's protocol. Levels of serum CA 125 (Roche Diagnostics Elecsys 2010, Chemiluminescent technology) and CK (Beckman synchon LX20 Pro, Enzymatic rate method) were also taken at presentation and 48 h later. The values at presentation and the change in levels after 48 h were used in the analysis. Women with complete data, i.e. serum measurements of both CA 125 and CK at 0 and 48 h, were included in the analysis.

All results were reviewed and followed up by the same primary investigator (G.C.). Exclusion criteria for the study were: (i) the visualization of any evidence of an intrauterine sac; (ii) identification of an adnexal mass thought to be an EP; (iii) the presence of heterogeneous, irregular tissues within the uterus thought to be an incomplete miscarriage; and/or (iv) women who were clinically unstable or the ultrasound scan revealed the presence of a haemoperitoneum. Indications for TVS included the presence of lower abdominal pain, with or without vaginal bleeding, a poor obstetric history or the need to determine gestational age. The women were followed up until a final outcome was established: i.e. a failing PUL, an IUP, an EP or a persisting PUL.

If the serum HCG rise over the 48 h period was >66% (Kadar *et al.*, 1981; Hahlin *et al.*, 1995), the women were classified as having an IUP and were rescanned 2 weeks later to confirm the diagnosis. If the initial serum progesterone level was <20 nmol/l, the women were classified as having a failing PUL (Banerjee *et al.*, 2001; Condous *et al.*, 2004a). Spontaneous resolution of the pregnancy was defined as a decrease in the serum HCG level to <5 IU/l with the disappearance of symptoms. Serum HCG levels were repeated within 7 days to confirm the diagnosis. The location of the failing PUL group remained unknown and this group were never visualized using TVS. An indeterminate proportion of these failing PUL are failing EP, as well as failing IUP. Women who did not fall into either category were reviewed every 48 h until a diagnosis was made by sonography.

The diagnosis of EP was based upon the positive visualization of an adnexal mass (Condous, 2004). Ultrasonographic diagnosis of an EP was based on the following grey-scale appearances: (i) an inhomogeneous mass adjacent to the ovary and moving separate to this—we have called this the 'blob' sign (Condous *et al.*, 2005a); or (ii) a mass with a hyperechoic ring around the gestational sac referred to as the 'bagel' sign (Condous, 2004); or (iii) a gestational sac with a fetal pole with or without cardiac activity (Condous, 2004). The diagnosis was subsequently confirmed at laparoscopy, in those treated surgically, with histological confirmation of chorionic villi in the Fallopian tube. If an EP was not visualized, but there was a high index of suspicion based on symptomatology, clinical findings and suboptimal rises of serial serum HCG levels, a laparoscopy was performed with or without an evacuation of the uterus.

The persisting PUL group behaves biochemically like EP and almost certainly represents ultrasonographically missed EP. These were included in the EP group for analysis.

Demographic data including age and gestation at presentation were also recorded.

Data analysis

The data have been pre-processed prior to further analysis. Several hormonal variables were created by transformation of the original variables. The first was the CA 125 ratio, i.e. serum CA 125 at 48 h/serum CA 125 at 0 h. The second transformed variable was the CK ratio, serum CK at 48 h/serum CK at 0 h.

Kruskal–Wallis tests were used to detect differences between all three outcome groups. Mann–Whitney tests were used for pairwise comparisons. Bonferroni corrections were used for multiple testing.

We incorporated the most significant of the variables, the CA 125 ratio, into a multinomial logistic regression model to predict all outcomes except persisting PUL, using the training data from the first 162 women. This model was tested on 135 PUL.

Receiver operating characteristic (ROC) analysis was performed to determine the effectiveness of this logistic regression model in predicting the failing PUL, IUP and EP. The ROC curve was constructed by plotting the sensitivity (true positive rate) versus 1 – specificity (false positive rate) for varying threshold values. The area under the ROC curves (AUC) can be statistically interpreted as the probability of the test to correctly distinguish the abnormal women from normal ones. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test. In this study, the AUC was obtained by a non-parametric method based on the Wilcoxon statistic, using the trapezoidal rule, to approximate the area and its associated standard error (DeLong *et al.*, 1988).

Statistical analyses were conducted with SAS (version 9 for windows, Leuven, Belgium).

Results

A total of 4698 consecutive pregnant women presented to the EPU during the study period; 403 (8.6%) consecutive women were classified with a PUL, 27 of these were lost to follow-up. Of the 376 women eligible, 297 had complete data for both serum CA 125 and CK levels recorded at 0 h and 48 h and these were analysed. The mean (± SD) age and gestation were 30.0 years (± 6.19) and 43.3 days (± 13.44) respectively. The final outcomes were 153 failing PUL (51.5%), 116 IUP (39.1%) and 28 EP (9.4%).

Table I presents the overall serum CK and CA 125 levels at 0 and 48 h, the mean serum CK and CA 125 and the CK and CA 125 ratios. The CK level at 0 and 48 h and the average CK level are positively skewed, with some extreme outliers. The CK ratio is rather symmetrical, but has some extreme outliers to the right. A similar picture emerges for the CA 125 measurements, but here the levels at 0 and 48 h and the average level are more heavily skewed to the right. This means that the variable has a far from symmetrical distribution, with a heavy tail on the right side. The CK and CA 125 do not change substantially over 48 h. 67.3% and 69.7% of the women's CK and CA 125 ratios respectively were between 0.8 and 1.2; 81.1% and 81.1% respectively were between 0.7 and 1.3; 91.2% and 89.9% respectively were between 0.6 and 1.4.

The statistics for each outcome group are also represented in Table I. There was no significant difference between the outcome groups when comparing absolute levels of CA 125 and CK as well as the trends of CK levels over 48 h. However, there seemed to be group differences for the CA 125 ratio ($P < 0.0001$) (Figure 1). The failing PUL group have a lower CA 125 ratio than either the IUP or EP groups. The difference

Table I. Biochemical characteristics of women with a pregnancy of unknown location (PUL)

	Total sample ($n = 297$)			Failing PUL ($n = 153$)			Intrauterine pregnancy ($n = 116$)			Ectopic pregnancy ($n = 28$)			P^a
	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR	
CK													
0 h	88.5	67.0	37.0	95.1	66.0	35.0	79.3	68.5	38.5	89.8	71.5	43.5	0.7782
48 h	86.8	66.0	37.0	85.9	67.0	43.0	86.7	64.0	27.5	92.0	66.5	43.0	0.6665
Mean	87.6	65.5	38.0	90.5	67.0	39.5	83.0	63.8	33.0	90.9	69.5	45.0	0.8656
CK ratio	1.05	0.98	0.27	1.05	0.99	0.26	1.06	0.97	0.29	0.98	0.96	0.25	0.3503
CA 125													
0 h	43.8	27.0	28.0	44.6	29.0	31.0	42.2	23.5	23.0	46.3	28.5	23.0	0.3343
48 h	40.1	26.0	26.0	37.5	25.0	24.0	43.2	25.0	31.0	42.0	30.5	24.5	0.6654
Mean	42.0	27.0	26.5	41.1	27.5	29.0	42.7	25.3	27.8	44.1	29.5	21.3	0.8864
CA 125 ratio	1.00	0.96	0.23	0.92	0.88	0.23	1.09	1.04	0.18	1.11	0.96	0.17	< 0.0001

[a]Kruskal–Wallis: non-parametric test for differences between the thee groups ($P < 0.05$ indicates statistical significance); pairwise comparisons for CA125 ratio indicate a clear difference between failing PUL and intrauterine pregnancy (IUP) ($P < 0.0001$) and between failing PUL and ectopic pregnancy ($P = 0.0028$), evidence for a difference between IUP and ectopic pregnancy is less clear ($P = 0.0378$); $P < 0.05$ indicates statistical significance, $P < 0.0167$ if Bonferroni correction for multiple testing is used.

CK = creatine kinase; CA 125 = cancer antigen 125; CK or CA 125 ratio = serum value 48 h/serum value 0 h; IQR = interquartile range representing range between 25th and 75th quartile.

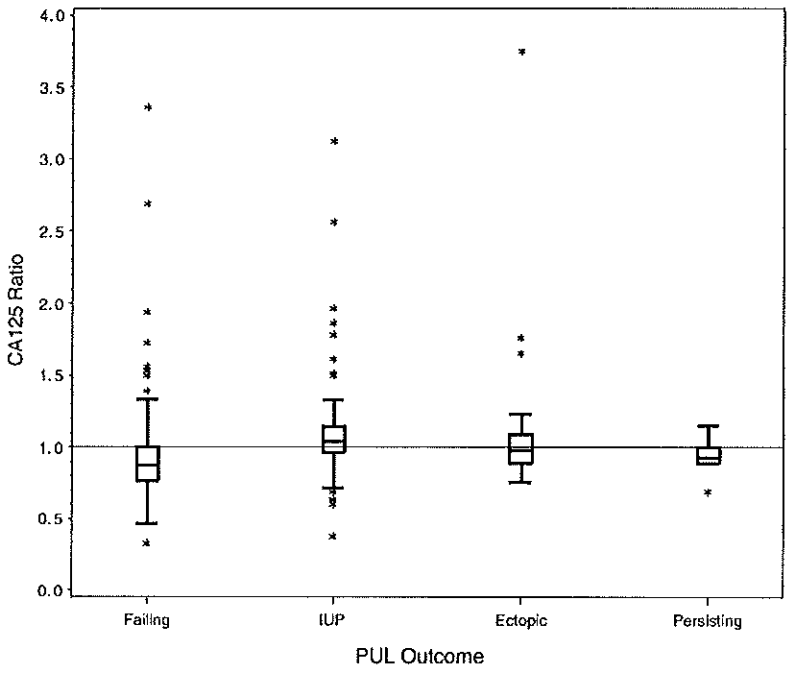


Figure 1. Box plot of cancer antigen 125 (CA 125) ratios for the four outcome groups.

between the IUP and EP groups is only borderline significant when Bonferroni corrections for multiple testing are used.

We incorporated the CA 125 ratio into a multinomial logistic regression model to predict the PUL outcomes, using a training set of the first 162 women [80 (49.4%) failing PUL, 68 (42.0%) IUP and 14 (8.6%) EP]. The effect of the CA 125 ratio was significant ($P = 0.0012$) and the model gave an area under the ROC curve of 0.697 (SE = 0.042) for a failing PUL, 0.703 (SE = 0.042) for an IUP and 0.478 (SE = 0.065) for an EP (Figure 2). This model was then tested on 135 PUL [73 (54.1%) failing PUL, 48 (35.6%) IUP and 14 (10.4%) EP]. This gave an area under the ROC curve of 0.782 (SE = 0.041) for a failing PUL, 0.768 (0.043) for an IUP and 0.560 (SE = 0.078) for an EP (Figure 3). We also developed posterior probability curves for each outcome based on the CA 125 ratio (Figure 4), which suggest that the CA 125 ratio can distinguish failing PUL from IUP. There seems to be little ability to detect EP. Note that very few observations fall outside the 0.6–1.4 range, so the curves are not highly reliable for values outside this range.

Discussion

This is the first study assessing the use of maternal serum CA 125 and CK in a PUL population. The baseline serum levels of these biochemical markers did not differ significantly between the three outcome groups, i.e. the failing PUL, immediately viable IUP and EP. Previous studies have evaluated the use of serum CA 125 levels in women who present at later gestations with confirmed IUP or extra-uterine pregnancies. Single serum measurements of CA 125 in such circumstances also fail to discriminate between EP, normal pregnancies and failing pregnancies (Schmidt *et al.*, 2001). Despite the difference in populations studied, the results are very similar.

Although the CK ratios (serum CK at 48 h/CK at 0 h) were not significantly different between the outcome groups, the change in serum CA 125 over time (CA 125 ratio) proved to be significant. The CA 125 ratio was significantly higher in the IUP and EP groups compared to the failing PUL group. In pregnancy, the tumour marker CA 125 is produced from the maternal decidua in response to the first wave of trophoblast invasion (Kobayashi *et al.*, 1989).

It has been well documented that serum CA 125 levels peak in the maternal serum at 6 to 7 weeks gestation (Check and Vetter, 1995). The timing of the first scan in this study, median gestational age of 41.0 days, corresponded with the first wave of trophoblast invasion in a pregnancy. Therefore it is not surprising that the CA 125 ratios were significantly higher in the IUP and EP groups compared to the failing PUL group, reflecting greater trophoblast invasion into the maternal circulation. The CA 125 ratios were not significantly different between the IUP and EP groups, which may reflect similar maternal decidual responses to these differently located pregnancies.

Maternal CK levels have been previously evaluated in confirmed EP (Korhonen *et al.*, 1996; Qasim *et al.*, 1996; Vandermolen and Borzelleca, 1996; Zorn *et al.*, 1997). CK is a non-specific marker of smooth muscle damage. The presence of trophoblastic tissue in the fallopian tube is thought to potentially result in damage to the smooth muscle of the fallopian tube, which in turn can increase maternal serum CK levels. However, maternal serum CK concentrations do not reliably predict confirmed EP (Korhonen *et al.*, 1996; Qasim *et al.*, 1996; Vandermolen and Borzelleca, 1996; Zorn *et al.*, 1997).

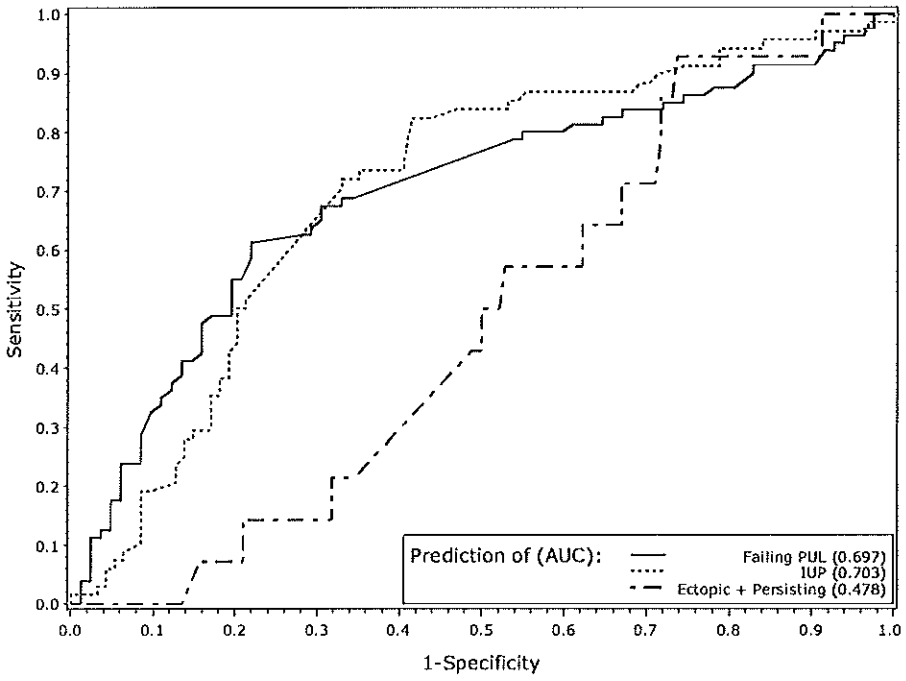


Figure 2. Comparison of receiver operating characteristic (ROC) curves for the prediction of failing pregnancy of unknown location (PUL), intrauterine pregnancy (IUP) or ectopic pregnancy + persisting PUL by using a multinomial logistic regression model (on 162 items of training data).

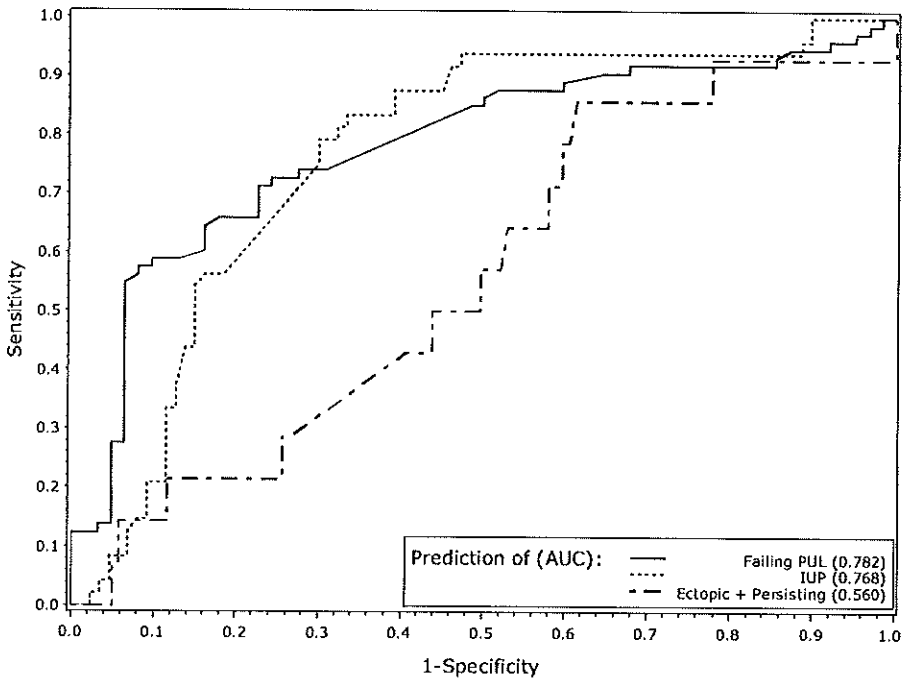


Figure 3. Comparison of receiver operating characteristic (ROC) curves for the prediction of failing pregnancy of unknown location (PUL), IUP or ectopic pregnancy + persisting PUL by using a multinomial logistic regression model (on 135 items of test data).

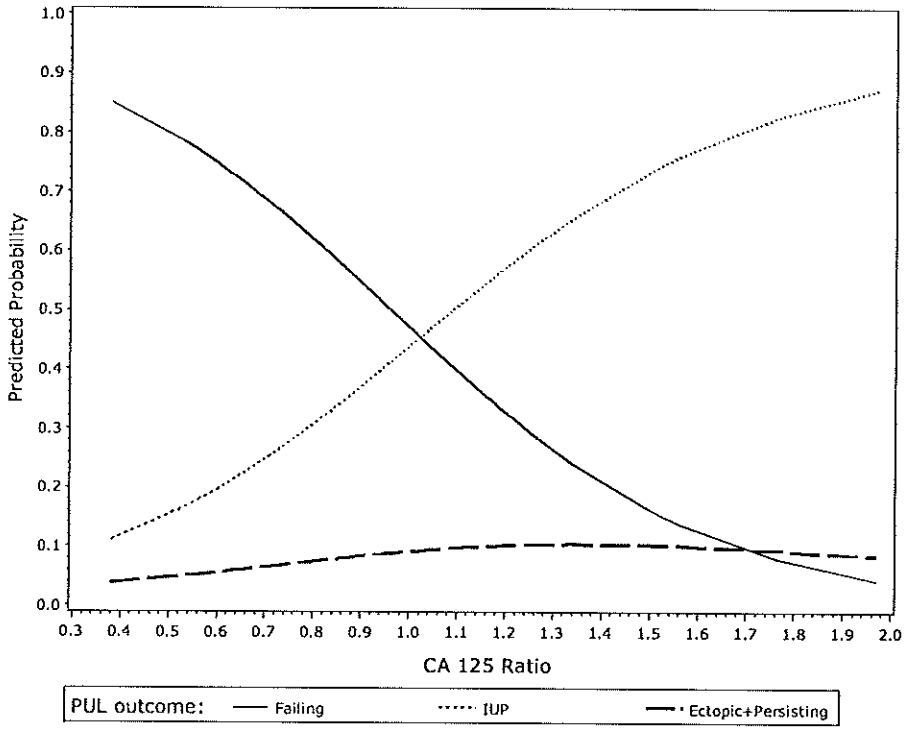


Figure 4. Posterior probabilities for a woman having a failing pregnancy of unknown location (PUL), an intrauterine pregnancy or an ectopic pregnancy versus the cancer antigen 125 ratio. The multinomial logistic regression model based on the training set gave the predicted probability.

In a PUL population, EP tend to be too early to visualize using ultrasound and in the absence of blood in the pouch of Douglas on TVS, one can expect that these EP are confined to the fallopian tube. Without clinical signs of tubal rupture being present, the likelihood of smooth muscle damage is negligible. One could hypothesize that, as all women in this study

were clinically stable at presentation with no signs of tubal rupture, and as there was no evidence of haemoperitoneum on ultrasound scan, serum CK levels would not be significantly higher in the EP PUL group compared to the others. This was indeed the case.

We believe that the use of the HCG ratio, i.e. the change in serum HCG levels over a 48 h period, and serum progesterone levels at presentation are still the best tools available in the management of PUL (Condous, 2004). According to a meta-analysis, serum progesterone measurement can identify women at risk for EP, but its discriminative capacity is insufficient to diagnose EP with certainty (Mol *et al.*, 1998). The incorporation of the HCG ratio into logistic regression analysis has been shown to significantly improve the detection rates of EP in women with a PUL (Condous *et al.*, 2004b). When incorporated into a multinomial logistic regression model in this study, the CA 125 ratio could distinguish failing PUL from IUP; however, it was not able to detect EP. The authors acknowledge that not all EP are dangerous and some resolve spontaneously without intervention (Ylostalo *et al.*, 1992; Korhonen *et al.*, 1994; Elson *et al.*, 2004). However, if one has a test that cannot predict the group of PUL that has the potential to cause the most harm, then it is difficult to ensure patient safety.

Laparoscopy is the gold standard for the detection of EP (Ankum *et al.*, 1993a). However, in a recent study in our unit, 90.9% of EP were diagnosed using TVS alone prior to surgery (Condous *et al.*, 2005a). TVS in combination with serum HCG levels is extremely useful as a diagnostic tool in suspected EP (Ankum *et al.*, 1993b). In an ideal study, in order to avoid any verification bias, all women should be subjected to the same gold standard. The universal use of laparoscopy would give an accurate prevalence of EP in a PUL population; however, it would be difficult to justify such an invasive approach on ethical grounds as the vast majority of PUL are non-EP (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999, 2001; Condous *et al.*, 2004). Therefore the use of non-invasive diagnostic techniques including serum hormone measurements and TVS were adopted for all three groups in this study (Ankum *et al.*, 1993b). The EP group also underwent laparoscopy for diagnostic confirmation as well as treatment. We accept that there was differential verification bias arising from selecting those women at high risk of EP for more invasive tests. Such shortcomings are justifiable in a clinical study where the vast majority of women with PUL are not only clinically stable but also relatively asymptomatic. We acknowledge, as was the case in a previous study (Condous *et al.*, 2005b), that such methodological flaws in doing any predictive studies on PUL are difficult to overcome.

We do not advocate immediate laparoscopic surgery even when an adnexal mass is noted on TVS. It is likely that some EPs with relatively low HCG levels will fail and so expectant management is an option. Apart from expectant management, medical therapy can be offered to women who are stable with rising or plateauing serum HCG levels. 28.2% of women with EPs in our unit undergo conservative management in the form of either expectant or methotrexate management. Of these 12.9% of women are managed expectantly and 15.3% are initially treated with methotrexate, the success rates being 59.5% and 72.7% respectively. As the number of women undergoing more conservative treatment modalities increases, as a consequence of ultrasound-based diagnoses, laparoscopy as the gold standard may become dispensable as a diagnostic tool.

According to our data, the routine use of serum CA 125 or CK in the management of women with PUL is not advocated. Absolute levels of maternal serum CA 125 and CK at the defined times cannot be used to predict the outcome of PUL. Although the CA 125 ratio incorporated into a logistic regression can distinguish failing PUL from IUP, its inability to detect the high-risk PUL, i.e. the developing EP, means its clinical role is limited.

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