

Prediction of ectopic pregnancy in early pregnancy of unknown location

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Prédiction de la grossesse extra-utérine en cas de grossesse jeune de localisation indéterminée

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R É S U M É

Prérequis : Les patientes ayant des grossesses jeunes de localisation indéterminée (GJLI) peuvent être définies comme celles ayant un test de grossesse positif en l'absence de visualisation de grossesse à l'échographie endo-vaginale (EEV).

But : Identifier les paramètres de diagnostic permettant de prédire la grossesse extra-utérine chez les femmes ayant des grossesses jeunes de localisation indéterminée

Méthodes : Nous avons mené une étude prospective observationnelle chez une population de femmes enceintes présentant des complications précoces de la grossesse. Quatre-vingt-quatorze patientes ont été classées comme ayant une grossesse jeune de localisation indéterminée après avoir réalisé EEV; un dosage sérique de l'hormone chorionique gonadotrophine humaine (-HCG) et de la progestérone sérique.

Toutes les données recueillies ont été testées par une analyse uni variée, puis analysées par régression logistique afin d'élaborer un modèle de qui prédit la grossesse extra-utérine.

Résultats : Un total de 2675 femmes ont été référées en cas de suspicion de complications précoces de la grossesse. Dans 94 (4%) cas la localisation de la grossesse n'était pas connu. Trois paramètres ont été identifiés statistiquement significatifs pour prédire la grossesse extra-utérine: le taux de progestérone, les métrorragies associés à la douleur et la présence d'un épanchement dans le Douglas. Le modèle global décrit par ces variables offre une sensibilité de 79% et une spécificité de 59% dans la prédiction de la grossesse extra-utérine.

Conclusion : Le modèle de régression logistique peut aider dans la prise de décision clinique chez les femmes présentant une grossesse jeune de localisation indéterminée.

Mots-clés

Grossesse jeune de localisation indéterminée, grossesse extra-utérine; échographie endovaginale.

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S U M M A R Y

Background: Women having pregnancies of unknown location (PUL) can be defined as those having positive pregnancy test when no pregnancy is visualized on transvaginal ultrasound (TVS).

Aim: To identify diagnostic parameters which are predictive of ectopic pregnancies in women with early pregnancies of unknown location.

Methods: We undertook a prospective observational study of pregnant women with suspected early pregnancy complications. Ninety-four patients were classified as having a pregnancy of unknown location (PUL) by transvaginal ultrasound; blood sample was taken on presentation to measure the serum human chorionic gonadotrophin (-HCG) and progesterone levels. All collected data were tested by univariate analysis and then analyzed in a stepwise procedure to form a logistic model for predicting ectopic pregnancy.

Results: A total of 2675 women were referred for suspected early pregnancy complications. In 94 (4%) patients the location of the pregnancy was unknown. Three parameters were found to be statistically significant for predicting ectopic pregnancy: progesterone level, vaginal bleeding associated with pain and the presence of free fluid in the pouch of Douglas. The overall model described by these variables offer a sensitivity of 79 %and a specificity of 59% in the prediction of ectopic pregnancy.

Conclusion: Logistic regression model can help in the clinical decision-making in women with pregnancy of unknown location.

Key- words

Pregnancy of unknown location; ectopic pregnancy; ultrasonography

Assessment of early pregnancy is indicated in women with suspected abnormalities such as miscarriage or ectopic pregnancy. It is based on biochemical assessment including serial measurements of serum levels of human chorionic gonadotrophin (β -HCG) and of progesterone [1], and on transvaginal sonography (TVS). TVS has been increasingly used as the method of choice for initial assessment of women with suspected early pregnancy complications [2, 3]. Women having pregnancies of unknown location (PUL) can be defined as those having positive pregnancy test when no pregnancy is visualized on TVS and there is no evidence of either an intra- or extra-uterine pregnancy or retained products of conception [4]. Management of these patients tends nowadays to be expectant, avoiding a great number of uterine instrumentations and unnecessary laparoscopies [5]. Ectopic pregnancy remains a leading cause of direct maternal death, and the incidence has progressively increased during the past years [6]. Early diagnosis may prevent tubal rupture, and allows elective or non-surgical treatment.

The aim of this prospective study was to assess the value of different clinical, ultrasound and hormone parameters in predicting ectopic pregnancy in a population of women with pregnancy of unknown location.

PATIENTS AND METHODS

We undertook a prospective observational study of pregnant women with suspected early pregnancy complications, who had been referred for an ultrasound scan by their general practitioners or the hospital consultant in the emergency department. A full history was taken and a thorough physical examination performed in all cases. All women underwent a transvaginal ultrasound examination with a 7.5 MHz probe (logic 400 pro series, GE ultrasound Europe; beethovenstrasse 239, 42665 solingen, Germany).

In a woman with a positive plasmatic test, a PUL was defined on the basis of transvaginal sonography if the endometrial cavity was empty with no evidence of an intrauterine gestational sac or of any retained products of conception and in the absence of visualized extra-uterine pregnancy.

Exclusion criteria included visualization of any evidence of an intrauterine pregnancy, identification of an adnexal mass that thought to be an ectopic pregnancy or blood in the pouch of Douglas on the initial scan, visualization of products of conception through the speculum and clinically unstable patients or those having an acute abdomen.

Peripheral blood sample was taken from these women to measure the levels of serum β -HCG (world Health organization, third international reference 75/537) and progesterone levels using ELFA (Enzyme linked fluorescent assay) technique (VIDAS®, bioMérieux®).

In our study the serum progesterone levels were expressed in ng/ml (nmol/l = 3.1796 ng/ml), serum β -HCG ≥ 25 IU/L represented a positive pregnancy test; no reference range was used for serum progesterone. Levels of β -HCG were measured again 48h later according to our protocol. The study protocol

was approved by the ethical committee of our hospital. All women gave their written informed consent. Follow-up consisted in monitoring the clinical features, serum hormone levels every 48 hours for β -HCG and transvaginal ultrasound findings until a final clinical diagnosis was established.

Expectant management of pregnancies of unknown location led to four possible outcomes.

Normal pregnancies were diagnosed when a gestational sac was visualized on TVS within the endometrial cavity. These women were rescanned seven to ten days later to confirm viability.

Miscarriage was diagnosed either histologically, following surgical evacuation of the uterus contents or on ultrasound examination in pregnancies that progressed to develop a demonstrable intrauterine gestational sac that subsequently failed in the first trimester.

Ectopic pregnancies were diagnosed on follow-up when TVS revealed an heterogeneous mass seen in the adnexal region adjacent to the ovary, a mass with a hyper echogenic ring around the gestational sac in the adnexal region, or the presence of an embryo with or without a heart beat in the adnexal region accompanied by raised serum levels of β -HCG.

The diagnosis was subsequently confirmed with laparoscopy and histological examination of the biopsy specimens. For women who received medical treatment for their ectopic pregnancy (intramuscular injection of a single dose of 1mg/kg of methotrexate), histological confirmation was not undertaken. Spontaneous resolution of pregnancy was defined by a decrease in serum β -HCG levels to < 25 UI/L with a complete resolution of symptoms without the need for any therapeutic intervention. The location of these pregnancies therefore remained unknown. Recorded data included the woman's age, past obstetric history and gestational age on presentation.

Recorded symptoms consisted of pain and bleeding. Recorded sonographic variables were endometrial thickness and the presence or absence of free fluid in the pouch of Douglas. Descriptive statistics were obtained for all four groups of data. Student's test, Mann-Whitney U test, one way analysis of variance, Kruskal – Wallis test and χ^2 test were used for statistical comparisons. A P value of < 0.05 was considered significant. Univariate and multivariate logistic regression analyses were carried out to identify clinical, biochemical and ultrasonographic parameters that were predictive of ectopic pregnancy. The tests were performed on computer using SPSS 11.5 for windows. A comparison of the predictive powers of the individual parameters and the final logistic equation was made by means of receiver operating characteristic (ROC) curves using Graph ROC for windows.

RESULTS

A total of 2675 consecutive women underwent ultrasonography for suspected early pregnancy problems, between August 2007 and February 2009. Normal intrauterine pregnancy was diagnosed in 1990 women (74%), miscarriage in 513 (19%) and ectopic pregnancy in 78 women (3%).

In 94 patients (4%) the pregnancy was not identified on the

initial ultrasound examination.

Among the 94 patients with PUL, 5 of them (5%) had a previous history of ectopic pregnancy, 27 (29%) had a previous history of miscarriage and 19 (20%) had a previous history of cesarean section.

Seventy-two women (77%) presented a lower abdominal pain at the initial visit, 62 patients (66%) had vaginal bleeding with or without abdominal pain and 86 women (91%) presented amenorrhea. Only 47 (50%) women presented with the triad amenorrhea, pain and bleeding.

At follow-up, among 94 women with PUL, there were 18 patients (19%) with normal intrauterine pregnancy, 17 patients (18%) with miscarriage of an intrauterine pregnancy, 19 cases (20%) of spontaneous resolution and 40 women (43%) with ectopic pregnancy. Twenty-eight 28 patients were treated successfully with systemic methotrexate and 12 patients underwent surgery by laparoscopy (radical treatment in 5 cases and conservative treatment in 7 cases).

Surgical interventions were required in only 15 cases (17%): three uterine curettages in the miscarriage group and 12 laparoscopies for treatment of ectopic pregnancy.

The average length of follow-up was 8.2days (range 1 to 32 days). Normal pregnancy was diagnosed after 4.6 days on

average (range 1 to 12 days). The diagnosis of miscarriage was made after 8.3days (range 4 to 16). A final diagnosis of spontaneous resolution of PUL was reached after 9.3 days (range 2 to 32). The diagnosis of ectopic pregnancy was carried out after 3.8 days (range 1 to 13 days). None of the ectopic pregnancies resulted in rupture and none of the women required blood transfusion.

There were significant differences in maternal age, duration of amenorrhea, incidence of vaginal bleeding and lower abdominal pain, endometrial thickness, β -HCG and progesterone levels among pregnancies of unknown location with different outcomes (table 1).

All parameters were tested using univariate analysis for predicting ectopic pregnancies. Three parameters were found to be statistically significant for predicting ectopic pregnancy: vaginal bleedings associated with pain progesterone level and the presence of free fluid in the pouch of Douglas (table 2).

Progesterone levels at the initial visit above 17.5 nmol/l can predict ectopic pregnancy in women with PULs with sensitivity of 74% and a specificity of 58%.

The overall model described by these variables was:

Probability of ectopic pregnancy = $1 / (1 + e^{-Z})$

When $Z = 1.524 \times \text{progesterone (ng/ml)} + 1.281 \times \text{bleeding}$

Table 1: The distribution of measured parameters in terms of final outcome

Variables	EP	IUP	SR	miscarriage	Significance of difference Between outcome group : P	
	n= 40 (43%)	n= 18 (19%)	n= 19 (20%)	n= 17 (18%)	Any differences	EP vs other outcomes
Age (years) *	30 [21.5-42.5]	27.2 [20.5 - 33.9]	32.9 [22.5 - 43.3]	31.7 [21.7 - 41.7]	0.003	0.202
Gravida***	2.55 [1- 7]	1.83 [0 - 4]	2.58 [1-6]	3.3 [1-10]	0.070	0.987
Para***	0.78 [0- 3]	0.56 [0- 3]	1.21 [0- 7]	1.3 [0- 4]	0.181	0.339
Amenorrhoea* (days)	43.16 [25.6 - 60.7]	41.7 [33.7 - 49.7]	42.8 [17.5 - 68]	56.6 [28.5 - 84.7]	0.001	0.221
Previous abortion #	5 [12.5]	0 [0]	3 [15.8]	3 [17]	0.194	0.603
Previous miscarriages#	13 [32.5]	5 [27.8]	4 [21.1]	5 [29.4]	0.590	0.329
Previous cesarian sections #	8 [20]	0 [0]	3 [15.8]	3 [17.6]	0.243	0.123
Previous ectopics #	3 [7.5]	1 [5.6]	1 [5.3]	0 [0]	0.682	0.294
Bleeding #	3 [7.5]	0 [0]	2 [10.5]	7 [41.2]	0.761	0.177
Pain #	9 [22.5]	11 [61.1]	1 [5.3]	1 [5.9]	< 0.001	0.820
Bleeding with pain #	26 [65]	3 [16.7]	12 [63.2]	8 [47.1]	< 0.001	0.032
Eudometrial*	10.7	15.2	9.3	11.8		
Thickness (mm)	[3.6-17.8]	[4.9-25.5]	[0.25-18.4]	[3.4-20.2]	<0.001	0.169
β -HCG (IU/l)**	836.8 [272-2569.5]	1719.5 [637-3856.7]	143 [96-583]	788.5 [236-1417.6]	0.014	0.464
Progesterone (ng/ml) **	10 [5.4-15.2]	15.5 [9.2-19.8]	1.3 [0.9-2.7]	1.5 [1.3-5.2]	<0.001	0.020
Free fluid in the pouch of Douglas #	10 [26]	2 [11]	0 [0]	1 [6]	N V	0.006

EP, ectopic pregnancy; IUP, intrauterine pregnancy; SR, spontaneous resolution; β -HCG, β -human chorionic gonadotrophin; NV, Not valid.

*: Data distributed normally .The values given are the mean and distribution to include 95 % normal range [\pm 1.96 standard deviation]**: Data distributed non parametrically .the values given are the median and interquartile range [25 th to 75 th quartiles];*** : Discrete data with mean and range;

#: Discrete data given as number with the variable present and [%] with the feature for each final outcome.

Statistic tests : -for percentages: Pearson's chi-square, -for means or medians Student's t test if data are normally distributed, Mann & Whitney test if data are not normally distributed

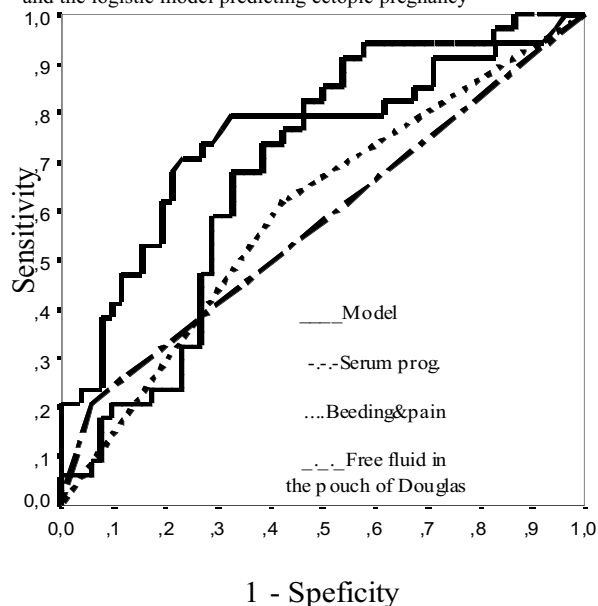
Table 2: Univariate analysis of predictors of ectopic pregnancy and comparison with logistic model

Variables	Area under the curve	SE	P Value	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Progesterone ng/ml (nmol/l)	0.69	0.057	0.003	5.50 (17.5)	0.74 (0.56-0.87)	0.58 (0.43-0.71)	0.54 (0.39-0.68)	0.77 (0.60-0.88)
Bleeding & pain	0.61	0.06	0.064	0/1	0.65 (0.48-0.79)	0.57 (0.43-0.71)	0.53 (0.38-0.67)	0.69 (0.53-0.81)
Free fluid in the pouch of Douglas	0.60	0.06	0.10	0/1	0.26 (0.14-0.42)	0.94 (0.84-0.99)	0.77 (0.46-0.94)	0.64 (0.52-0.74)
Logistic model	0.75	0.06	< 0.001	0.37	0.79 (0.62-0.91)	0.59 (0.42-0.73)	0.61 (0.46-0.75)	0.77 (0.59-0.90)

AUC: Area under the ROC (receiver operating characteristic) curve ;SE : Standard error; PPV : positive predictive value ; NPV : Negative predictive value.
 Logistic model provides the probability of the event using the equation: $p = 1 / 1 + e^{-Z}$, in which $z = ,*x1 + ,*x2 + ,*x3...+ ,*xn +$, constant

&pain score + 1.431 x free fluid in the pouch of Douglas - 2.136.

Prediction of ectopic pregnancy based on initial parameter considered separately such as initial serum progesterone level, was as accurate as prediction based on more complex multi-parameter models (figure 1).

Figure 1: Receiver operating characteristic curve for each parameter and the logistic model predicting ectopic pregnancy

DISCUSSION

Transvaginal ultrasound is an accurate diagnostic procedure for women with suspected early pregnancy complications. It enables diagnosis of location of these pregnancies in greater

than 90% of cases [3, 7]. Diagnosis by ultrasound can be optimized with the use of high-quality ultrasound equipment, experienced sonographers, and prior knowledge of risk factors and symptoms of ectopic pregnancies [8].

In this study accurate location of the pregnancy was determined at the initial visit in 96% of cases. The international society of ultrasound in obstetrics and gynecology states that early pregnancy units should try to maintain a PUL rate at less than 15% [9].

Reported incidence of PUL can range from 7 up to 31% [9-12]. Expectant management of PULs has been shown to be safe for the majority of asymptomatic hemodynamically stable women [10-12].

Only some cases require diagnostic laparoscopy or uterine curettage to determine the location of the pregnancy but there is no consensus on what is an acceptable intervention rate in this group. In this study, only three women (3%) required surgical interventions. Twelve (13%) laparoscopies were performed to treat ectopic pregnancies.

Published data show that 7- 20% of PULs will subsequently be diagnosed with an ectopic pregnancy [10-13]. However, a proportion of pregnancies that resolve spontaneously will be failed ectopic pregnancies since the true location will never be known. In our study the rate of ectopic pregnancies was relatively high reaching 43% of cases .Similar percentages have been reported (36-42.8%) [14, 15]. In fact the prevalence of ectopic pregnancy in a PUL population reflects the quality of scanning and the extent of the operator's experience .Women with EP in a PUL group will be classified as having a PUL or having inconclusive scans [16].

Bleeding associated with pain appears to be a significant parameter in prediction of ectopic pregnancy at univariate analysis: OR= 3 (IC 95%; 1.07 – 5.82; P = 0,032), Condous et al [9] concluded in their study that bleeding was the most significant clinical parameter to distinguish between different outcomes.

Bleeding alone or lower abdominal pain alone did not appear to

be a significant parameter in predicting EP. The absence of bleeding was associated with ectopic pregnancies in 27% of cases and in 83% of intra uterine pregnancies. The absence of pain was associated with 12% of EP, 22% of IUP and 32% of SR.

So, asymptomatic women with PUL should be followed up carefully because the diagnosis of EP could not be eliminated and the risk of serious complication should be considered.

A single β -HCG measurement is of limited value to predict the outcome of PUL [17] because of a significant overlap between levels. The concept of a discriminatory level of β -HCG was developed to predict ectopic pregnancy. The combination of serum β -HCG levels above a certain "discriminatory level" and the absence of IUP on scan is used as an indication for diagnostic laparoscopy.

This practice can fail to diagnose ectopic pregnancies since more than 50% of ectopic pregnancies in the PUL group will have initial serum β -HCG levels below the lowest used discriminatory levels [18]. Therefore, using laparoscopy as a diagnostic tool should be a rare event.

Multiple discriminatory levels were tested for the prediction of ectopic pregnancy in women with PUL (1000, 1500 and 2000 IU/L), but the sensitivity decreased as the discriminatory level of β -HCG increased [19].

Serial titers of serum β -HCG can be used to predict different outcomes within the PUL population; a minimal rise of 66% in 48 hours to predict an IUP was described [20] however; recently a more conservative cut-off of 35% has been suggested in order to minimize the risk of interruption of a viable pregnancy [21].

The pattern of β -HCG changes in ectopic pregnancies is difficult to characterize as 20% of EP will have a doubling serum HCG time similar to that of IUP. In 8% of EP, β -HCG profiles will mimic a failing PUL [22]. In this study 2.5 % of patients with ectopic pregnancy had a serum β -HCG level under 1000IU/L.

Serum progesterone levels are used to help predict the outcome of PULs. A high progesterone level reflects a normally functioning corpus luteum of a viable pregnancy.

Levels of less than 20 nmol/L have been shown to have a positive predictive value of greater than 95% for the prediction of pregnancy failure [12]. Levels above 60nmol/L are strongly associated with viable pregnancies [4].

A recent meta-analysis of 26 studies [23] has demonstrated that a single progesterone level seems to be good at predicting pregnancy viability but it is not so accurate at predicting pregnancy location. Studies have shown that 2% to 29% of ectopic pregnancies may be viable with serum progesterone levels above 60nmol/L [7, 24, 25].

In this study, thirty-six women (41.4%) with a pregnancy of unknown location had initial serum progesterone levels between 20nmol/L and 60nmol/L. In this group, 20 patients (55.6%) had an ectopic pregnancy and 11 patients (30.6%) had an IUP. Therefore, progesterone levels are poor at predicting pregnancy location, and careful follow-up must be organized in women with high progesterone levels until diagnosis of final outcome.

Another algorithm to diagnosis EP based on the use of pelvic ultrasound to demonstrate the absence of an intrauterine sac followed by uterine curettage, after a viable pregnancy has been excluded. According to this protocol if serum β -HCG fails to decrease by more than 15% after curettage or increases 8-12 hours after curettage, a diagnosis of ectopic pregnancy is assumed [26, 27].

This protocol may lead to intervention in some viable IU pregnancies. The limited value of uterine curettage for the diagnosis of ectopic pregnancy has also been reported [28]. According to a recent study, uterine evacuation can be useful in distinguishing between ectopic pregnancy and spontaneous abortion in women with non viable PUL: a >30% fall in post curettage β -HCG level was suggestive, but not diagnostic of spontaneous abortion [10].

Mathematical models have been developed to predict the outcome of PUL [1, 10, 11, 29]. These models, like in clinical practice combined various parameters to formulate diagnosis. Their use in clinical decision making is likely to improve management of PUL. They can be used as a rationale for the follow-up of PUL. However, a prospective validation with multicenter trials is necessary to evaluate their diagnostic performance in different populations [16].

A prospective study performed with the aim of diagnosing IUP and ectopic pregnancies on the basis of three visits within 7 days and failing PUL on the basis of two visits within 2 days, showed that 97.5% of women were given a diagnosis within 7 days [13]. By measuring the area under the receiver operating characteristic curve we realized that there was no statistically significant difference between the regression logistic model and the other significant parameters at the univariate analysis in predicting ectopic pregnancies. A serum progesterone level at the initial visit above a cut-off of 17.5 nmol/L (5.5 ng/ml) will predict EP with an OR=4 (IC 95%, 1.54-10.05, P = 0.03), this measurement achieved a sensitivity of 74% and a specificity of 58%.

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