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Outcome prediction in pregnancies of unknown location using endometrial thickness measurement: is this of real clinical value?☆

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ABSTRACT

Objective: To re-evaluate the role of measuring endometrial thickness (ET) in prediction of intrauterine pregnancy (IUP) among women with pregnancy of unknown location (PUL).
Study design: 987 women with PUL were included in a prospective observational multicenter study. Transvaginal ultrasonography was performed to measure ET and a blood sample was taken to measure serum β-hCG and progesterone levels. All patients were then managed expectantly till the final PUL outcome was diagnosed.
Results: 78 patients (8.9%) were finally diagnosed as having IUP. The best cutoff point of ET as a possible predictor for IUP was 10 mm, with an area under receiver-operating characteristic (ROC) curve of 69.0%. At this cutoff point, ET was able to predict IUP with positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of 1.43 and 0.19, respectively. Serum progesterone at a cutoff point of 50 nmol/L was able to predict IUP with PLR and NLR of 9.0 and 0.06, respectively. Variables showing statistically significant differences among those with IUP and those with the other PUL outcomes using univariate analysis (ET, gestational age, β-hCG, parity, serum progesterone and maternal age) were entered into logistic regression analysis. Logistic regression models were constructed. The performance of these models was better than using ET alone to predict the outcome of PUL.
Conclusion: Measurement of ET is not recommended as a single clinical test for intrauterine pregnancy prediction in women with pregnancy of unknown location.

1. Introduction

Pregnancy of unknown location (PUL) describes the presence of a positive pregnancy test without any evidence of intrauterine or extrauterine pregnancy seen on transvaginal ultrasonography (TVS) [1]. PUL is estimated to occur in about 8–31% of pregnancies [2–7]. There are four recognized clinical fates of PUL: failing PUL (FPUL), intrauterine pregnancy (IUP), ectopic pregnancy (EP) or persistent PUL (PPUL) [8]. Expectant management is the usual rule in managing PUL as it is safe and decreases the need for performing unnecessary surgical interventions [9].

Few studies have tried to use the endometrial thickness (ET) as a single predictor for PUL outcome. It was assumed that increased ET is associated with an early developing intrauterine gestation, but there was considerable overlap of ET values [10,11]. This study investigated factors that may give clue to the diagnosis of PUL outcomes, including measurement of ET and progesterone and β-hCG levels.

2. Materials and methods

A prospective observational multicenter study was carried out through the Early Pregnancy Assessment Units of three large government hospitals during the period from 1st July 2009 to 30th January 2012. The study protocol was approved by the hospitals' local ethics and research committees. A total of 987 pregnant women with PUL were initially recruited in the study. The diagnosis of PUL was based on having a positive pregnancy test with no evidence of an intrauterine or extrauterine pregnancy on the transvaginal scan. The following patients were excluded from the study: patients who had a query intrauterine gestational sac, patients who had an adnexal mass, hemodynamically unstable patients, patients with evidence of hemoperitoneum, patients with products of conception seen on vaginal examination and patients giving history of passing products of conception seen by a healthcare provider and sent for histopathological examination.

☆ *Setting*: Multicenter study (Early Pregnancy Assessment Units of 3 large governmental hospitals in 3 different regions in Saudi Arabia; eastern, northern and southern regions).

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A full history was taken in all cases, and then a thorough clinical examination was performed. All women had a positive urine pregnancy test (Clinitest® β-hCG Pregnancy Test with Clinitek Status Analyzer). This test can detect a level approximating ≥ 25 mIU/mL β-hCG with clinical accuracy > 99%. Transvaginal ultrasound scanning (Voluson 730 Pro© 2004, General Electric Healthcare Company, USA) was then performed using a 5-MHz transvaginal probe to measure ET (measured in the longitudinal plane at the point of maximum thickness) and to exclude the presence of an intrauterine or extrauterine gestational sac, adnexal masses, and hemoperitoneum. A blood sample was then taken to measure serum β-hCG and progesterone levels using an automated immunoassay system (Advia Centaur®, Bayer Diagnostics, Tarrytown, NY, USA). Serum β-hCG was measured using the total β-hCG two-side sandwich immunoassay with a detection range of 2–1000 mIU/mL: if a level of >1000 mIU/mL was encountered, the assay was repeated after a dilution step to allow up to 100,000 mIU/mL to be detected. The inter-assay and intra-assay coefficients of variation were 2.9%, and 2.8%, respectively. For serum progesterone measurement, the progesterone competitive immunoassay using direct chemiluminescence was used with a detection range of 0.48–190.8 ng/mL with inter-assay and intra-assay coefficient of variation of 3.6% and 5.3%, respectively.

Patients were then managed expectantly with serial measurements of serum levels of β-hCG. A printed patient information sheet was given to all patients including all the information about pregnancy of unknown location and the essential instructions and precautions. The follow-up visits were scheduled according to the patient condition and were continued till the final diagnosis and treatment were achieved.

Abnormal β-hCG patterns or worsening clinical symptoms were the cutoff point for need of intervention and stopping expectant management. Abnormal β-hCG pattern was defined as 3 measurements taken 48 h apart showing suboptimal increase or decrease (i.e. less than 66% increase or less than 15% decrease), plateauing, or fluctuating β-hCG levels.

The IUP group was identified during follow-up by the presence of a gestational sac eccentrically placed within the endometrial cavity in the TVS. The portion of the ectopic pregnancy group who had surgical intervention for their ectopic pregnancy was identified laparoscopically and by histological examination of the surgical specimen. The other portion of the ectopic pregnancy group who received medical treatment was identified only sonographically without histological confirmation. The diagnosis of an EP sonographically was based on the positive visualization of an adnexal mass based on the following gray-scale appearances: (i) an inhomogeneous mass adjacent to the ovary and moving separate to it (the blob sign); or (ii) a mass with a hyper-echoic ring around the gestational sac (bagel sign) or (iii) a gestational sac with a fetal pole with or without cardiac activity [12]. A failing PUL (FPUL) group was identified when there were persistent negative sonographic findings in the presence of falling serum β-hCG levels; ultimately reaching the undetectable levels (i.e. lower than 5 U/l). The persistent PUL (PPUL) group was identified in those women where serum β-hCG levels failed to decline and the location of the pregnancy could not be identified using TVS.

The required sample size was estimated using PASS© 2005 (NCSS, LLC, Kaysville, Utah, USA). The primary outcome measure was the percentage of women with IUP. Review of our institutional databases indicated that the percentage of IUP was approximately 10%. Thus, it was estimated that logistic regression of a binary response variable (Y) on a continuous, normally distributed variable (X) with a total sample size of 800 observations would achieve 90% power at a 0.05 significance level to detect a change in Prob($Y = 1$) from the value of 0.1 at the mean of X to 0.14 when X is increased to one standard deviation above the mean. This difference corresponded to an odds ratio of 1.5.

Statistical tests were made on an IBM-based computer with the use of SPSS (Statistical package of Social Sciences) version 15.0, Medcalc version 11.6.1, Epicalc 2000, and Microsoft Excel 2003.

The normality of distribution of numerical data was tested using the one-sample Kolmogorov–Smirnov test and inspection of histograms of frequency distribution. Skewed data were presented as median (interquartile range) and between-group differences were compared non-parametrically using the Mann–Whitney test with Bonferroni correction for subgroup comparisons. Pearson's correlation was used in order to identify the direction and the power of correlation among each couple of the studied variables. Receiver-operating characteristics (ROC) curves evaluated the cutoff point and performance of the different possible predictors of normal location pregnancy. Performance was expressed in the form of sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and accuracy.

Variables showing statistically significant differences ($P < 0.05$) between the studied groups on univariate analysis (maternal age, parity, estimated gestational age (EGA) by last menstrual period (LMP), ET, serum progesterone level and serum β-hCG level) were entered in logistic regression analysis. All selected predictors were forced into the model to develop a model that would predict IUP using the 'enter' method to avoid elimination of pertinent predictors. To examine the predictive value of the model, a ROC curve was plotted and the area under the curve (AUC) was estimated.

3. Results

The study statistical analysis included 872 women (Fig. 1). PUL patients were classified based on the final outcome into two main

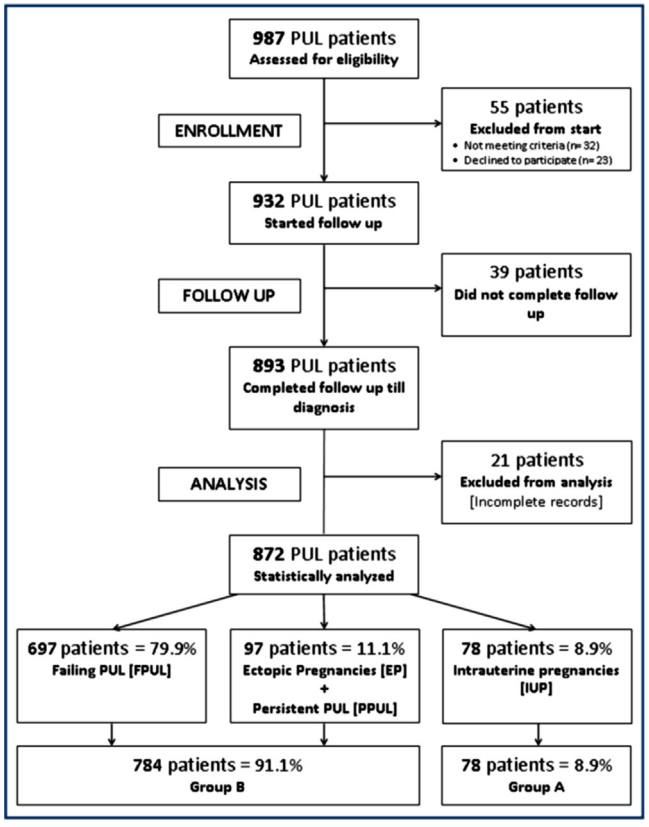

Fig. 1. Patient flow chart.