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Serial hCG and progesterone levels to predict early pregnancy outcomes in pregnancies of uncertain viability: A prospective study

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ABSTRACT

Objective: To assess the value of serial hCG and progesterone serum level in the diagnosis of early pregnancy viability.
Methods: It was a prospective cohort study. Women with a pregnancy of uncertain viability (PUV), defined as the presence of an intra-uterine embryo with a crown-rump length <7 mm with no cardiac activity or an intra-uterine gestational sac size <25 mm with no visible embryonic structure in a transvaginal ultrasound scan (TVS) were eligible. The diagnosis value of serial plasmatic hCG levels on the first day and 48 h after as well as the initial progesterone level were evaluated to diagnose pregnancy viability. Pregnancy viability was assessed by TVS 7 to 14 days after inclusion.
Results: The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of an hCG H48/H0 ratio increase <11% to diagnose an early pregnancy loss were 70.6%, 100%, 100% and 85.3%, respectively. The sensitivity, specificity, PPV and NPV of a 6.2 ng/ml progesterone level to diagnose an early pregnancy loss were 20%, 100%, 100% and 65.2%, respectively. The sensitivity, specificity, PPV and NPV of an hCG H48/H0 ratio increase >75% to diagnose a viable pregnancy were 100%, 31%, 45.9% and 100%, respectively. hCG H48/H0 ratio increase <11% was associated with early pregnancy loss in 100% of the cases. hCG H48/H0 ratio increase >75% was associated with 100% of viable pregnancies in 100% of the cases.
Conclusion: Serial hCG levels alone permitted an early viability diagnosis within 48 h for 41.1% of patients with PUV instead of 7 to 14 days with TVS.

Introduction

Early pregnancy loss occurs in approximately 10 to 15% of pregnancies and affects one in three women [1,2]. It is associated with considerable human and financial burdens [3]. Symptomatic early pregnancy requires huge public health costs and has huge anxiety costs.

When vaginal bleeding or pelvic pain occurs in the first trimester, the first step is to exclude an ectopic pregnancy. Once it is excluded, the second step is to diagnose pregnancy viability. When empty gestational sac (GS) or fetal pole with no cardiac activity is found using vaginal sonography, ectopic pregnancy is excluded (unless a heterotopic pregnancy is present), but the viability of the pregnancy cannot be confirmed or excluded in the first examination and requires further investigation. A pregnancy of uncertain viability (PUV) is defined by the presence in a transvaginal ultrasound scan (TVS) of an intrauterine gestational sac with no embryonic heartbeat (and no findings of definite pregnancy failure), that is an intra-uterine embryo with crown-rump length (CRL) <7 mm with no cardiac activity or mean GS diameter of 16–24 mm and no embryo[4].

Markers such as patient age, miscarriage history, symptoms, gap between theoretical and TVS gestational age, slow CRL kinetic, GS size or YS (Yolk sac) size, the presence of hematoma can predict miscarriage. However they cannot confirm the diagnosis alone or using a score[5]. Pregnancy viability diagnosis for PUV requires a repeat TVS examination. Depending on the first TVS finding, TVS will be repeated between 7 and 14 days later [6–8]. The absence of

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an embryo with cardiac activity within 7 or 14 days establishes the diagnosis of early pregnancy loss. As shown in a recent study by Richardson et al., diagnostic uncertainties in early pregnancies are highly anxiogenic and require an immediate positive or negative diagnosis[9]. No alternatives to a second TVS one to two weeks later have been suggested to decrease the period of uncertainty.

Serial hCG or progesterone are used for pregnancy of unknown location (PUL) diagnosis[10]. Their use has reduced morbidity and mortality for ectopic pregnancies[7]. However, the use of hCG and progesterone have not yet been evaluated for PUV. The objective of this study was to determine the diagnosis performance of serial serum hCG levels and progesterone level for the diagnosis of viability.

Materials and methods

Study design

We conducted a prospective single-center observational study including consecutive pregnant women with PUV in the early pregnancy unit of a tertiary teaching hospital between 01/05/2015 and 01/05/2016. Informed consent was obtained. The local institutional review board approved the study (IRB, France Avis n° 16.84). Written informed consent was obtained from each patient before inclusion in the study.

Patients

Pregnant women with symptomatic PUV who were older than 18 years old were included. Symptoms included pain and/or bleeding. PUV was defined with TVS using the following findings: intact intra uterine GS <25 mm (mean of three orthogonal measures) with no visible embryonic structure; intrauterine GS containing an embryo with CRL <7 mm with no cardiac activity, as defined by guidelines[4,7,8].

Protocol

Women with symptomatic pregnancy had a TVS (Philips HD7xe®, USA) performed by a senior gynecologist or by a resident under supervision of a senior gynecologist. Patients who met the inclusion criteria were eligible for the study and had both oral and written explanations about the study provided by physicians. After they signed the informed consent, the patients were included.

Each patient underwent a blood sample for serum level of hCG and progesterone on the first day (H0) and serum hCG was measured 48 h after (H48). According to the French National and international recommendations for management of PUV [7,8,11], viability was checked by a repeat TVS that was performed 14 days after in cases of a GS without any visible embryonic structure or YS, 11 days in cases of a GS with YS and no embryo, and 7 days in cases of an embryo <7 mm with no cardiac activity. Depending on the ultrasound findings during repeat TVS, the diagnosis of viable pregnancy or early pregnancy loss was performed. The viable pregnancy was defined by an embryo with cardiac activity. Early pregnancy loss was defined by no visualization of cardiac activity in the repeat TVS.

Serum level of plasmatic hCG and progesterone were measured with Roche hCG and the Progesterone II Electrochemiluminescence Assay (ECLIA), respectively, on a Roche Cobas e411 and e602 analyzer. The inter-assay CVs for hCG and progesterone were, respectively, <5.2% and <7.5% in our laboratory.

The following data were recorded: patient age, parity, gravidity, history of miscarriage, vaginal bleeding, pain, and initial US findings.

Patients who did not come to the repeat TVS were considered to be lost to follow-up.

Outcomes

The primary outcome was viable pregnancy defined by an embryo with cardiac activity in a TVS at the last follow-up control day (7, 11 or 14 days). The secondary outcome was pregnancy loss defined by the absence of an embryo with cardiac activity on TVS at the 7, 11 or 14 follow-up control days.

Statistical methods

Data were collected through numeric medical files. Differences between groups were assessed using the chi square test or Fisher's exact test for categoric variables and Student's *t*-test for continuous variables. p values smaller than 0.05 were considered significant. Results were expressed as percentages or the mean ±SD. Univariable logistic regressions were expressed with Odd Ratios and 95% confidence intervals. The ROC curve was plotted to determine the optimal hCG and progesterone cut-offs. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the tests were calculated for various cut-offs.

Results

Patient inclusion and follow-up

Between 01/05/2015 and 01/05/2016, 1435 pregnant women in the first trimester of gestation attended the pregnancy emergency unit for pain/vaginal bleeding. In 179 (12.5%) patients, the viability

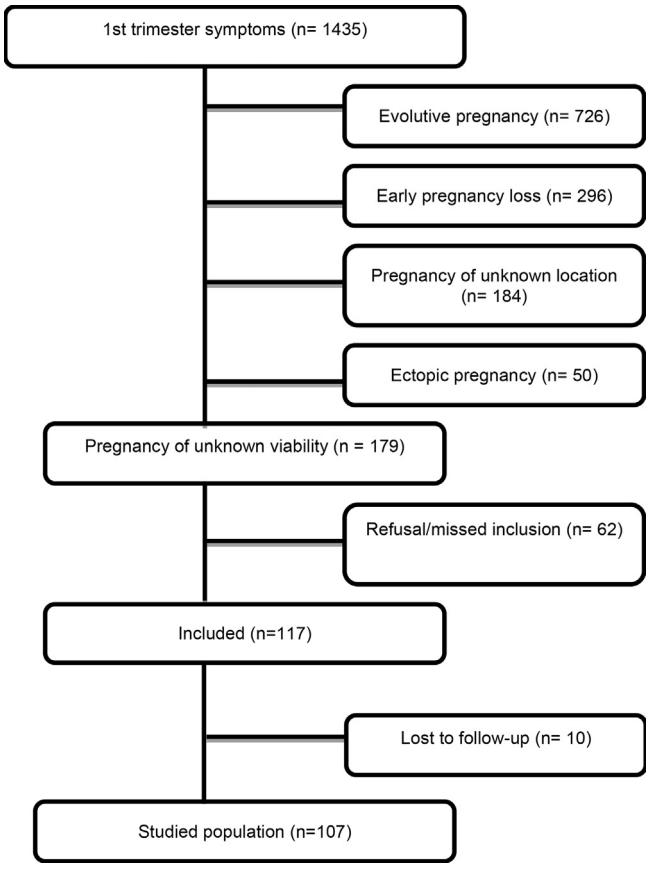

Fig. 1. Flow Chart.