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Same-day confirmation of intrauterine pregnancy failure in women with first- and early second-trimester bleeding

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Objective: To determine if alpha-fetoprotein (AFP) concentration in vaginal blood, in the setting of dissolved fetal tissue, is significantly higher than its concentration in the maternal serum.
Design: A prospective cohort study.
Setting: Medical center.
Patient(s): Four groups of women were evaluated: 1) with missed/incomplete miscarriage with vaginal bleeding; 2) with threatened miscarriage; 3) with vaginal bleeding during cerclage placement; and 4) undergoing dilation and curettage (D&C).
Intervention(s): None.
Main Outcome Measure(s): In each patient, AFP concentration in the vaginal blood or in the liquid component of the evacuated products of conception (POC; D&C group) was compared with the AFP concentration in the maternal serum.
Result(s): The median (range) concentration ratios of AFP in vaginal blood (or POC) to AFP in maternal serum were 24.5 (5.1–8,620) and 957 (4.6–24,216) for the missed/incomplete (n = 30) and the D&C (n = 22) groups, respectively, whereas they were only 1.2 (0.4–13.4) and 1.01 (0.7–1.5) for the threatened miscarriage (n = 15) and cerclage (n = 9) groups, respectively. Receiver operating characteristic (ROC) analysis demonstrated 100% sensitivity and 86.7% specificity for the detection of the passage of fetal tissue (ratio 4.3, area under the ROC curve 0.96).
Conclusion(s): Higher concentrations of AFP in vaginal blood than in maternal serum may indicate the presence of dissolved fetal tissue (i.e., confirming a failed pregnancy). (Fertil Steril® 2018;109:1060–4. ©2018 by American Society for Reproductive Medicine.)
Key Words: Alpha-fetoprotein, miscarriage, rapid test

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Differentiating between an early intrauterine pregnancy (IUP) failure (missed or incomplete miscarriages), a threatened miscarriage, and an extrauterine pregnancy (EUP) can be challenging. Often, serial clinical evaluations, transvaginal ultrasounds, and quantitative β-hCG levels are needed to reach a final diagnosis. Multiple biomarkers have been used to detect an EUP or to predict the likelihood of a failing IUP (1–3). However, to date, there is no reliable same-day laboratory test that can confirm the presence of an IUP (in the case of a pregnancy of unknown location) and determine if it is failing (in the case of first-trimester bleeding).

Alpha-fetoprotein (AFP) is produced by the yolk sac and later on by the fetal liver (4). In the first trimester, as early as the 5th week of gestation, AFP concentration can be measured from the embryonic tissue. It has been shown that AFP in the fetal serum is $\geq$1,000 times higher than in the maternal serum at any gestational age (5). The objective of the present study was to determine if AFP concentration

Received August 22, 2017; revised and accepted February 2, 2018.
A.M. and Maimonides Medical Center are co-owners of a provisional patent describing the presented diagnostic technique. R.T. has nothing to disclose. S.H. has nothing to disclose. B.K. has nothing to disclose. S.H.N. has nothing to disclose. H.M. has nothing to disclose.
Supported by the Maimonides Medical Center Research Foundation, award no 49822.
Presented as an abstract at the American College of Obstetricians and Gynecologists annual meeting, Washington, D.C., May 2016. The abstract received the Blue Ribbon award.
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Fertility and Sterility® Vol. 109, No. 6, June 2018 0015-0282/$36.00
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https://doi.org/10.1016/j.fertnstert.2018.02.006

in vaginal blood that contains dissolved fetal tissue is higher than the AFP concentration in maternal serum. In other words, we sought to determine whether a relatively high concentration of AFP in first-trimester (or early second trimester) vaginal blood confirms the presence of an IUP that has failed (a missed or an incomplete miscarriage).

MATERIALS AND METHODS

This study was designed and conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines. The study protocol was approved on February 5, 2016, by the Maimonides Medical Center Institutional Review Board (project number 2013-11-25). Written consents were obtained from all study participants before their participation. This prospective cohort study was performed from February 2016 to March 2017. Pregnant women in their first and second trimesters were recruited at the Maimonides Medical Center (MMC) Labor and Delivery Department (convenience sample). Maternal and vaginal blood (with or without fetal tissue) samples were collected from all research participants at the MMC Labor and Delivery Department.

The inclusion criteria were single intrauterine pregnancy confirmed by means of transvaginal ultrasound and the collection of maternal (venous) and vaginal blood specimens up to 1 hour apart. Four groups were evaluated, as follows. 1) The missed/incomplete miscarriage group included women with missed or incomplete miscarriage who had vaginal bleeding. We followed the diagnostic criteria for a nonviable IUP provided by Doubilet et al. (6). Our definitions were as follows: Incomplete miscarriage was defined as bleeding that has begun and the cervix is dilated, but tissue from the pregnancy still remains in the uterus. Missed miscarriage included the following: yolk sac miscarriage, embryonic miscarriage, and fetal miscarriage, according to the definitions by Kolte at al. (7). 2) The threatened miscarriage group included women with vaginal bleeding who had a documented IUP with an embryo or fetus with cardiac activity. 3) The cerclage group included women with vaginal bleeding during cervical cerclage placement (a negative control group for the passage of fetal tissue; fetal cardiac activity was demonstrated before and after the procedure). And 4) The dilation and curettage (D&C) group included women with confirmed IUP (viable or nonviable) undergoing D&C (a positive control group for passing fetal tissue). For the missed/incomplete and threatened miscarriage groups, as well as the cerclage group, $\geq$1 mL of vaginal blood exiting the introitus was collected into a cup and then transferred to a serum-separating tube. Within an hour, the tube was transported to the MMC chemistry lab for vaginal AFP concentration quantification by means of a chemiluminescent immunoassay (Beckman Coulter Life Sciences).

The indications for cerclage were obstetrical and based on patient's history, physical exam, and/or ultrasound findings (8). Regarding the D&C group, the products of conception (POC) were collected in a suction container. By the end of the suction D&C procedure, fetal tissue as well as maternal and fetal blood were present in the suction container. The fetal tissue was sent for histopathologic evaluation and 1 mL of the collected blood (the liquid component) was transported to the MMC laboratory for AFP quantification as described above.

The confirmation of an IUP was done through a histopathologic review of the specimens evacuated from the vagina or uterus (missed/incomplete and D&C groups) or with the use of ultrasound (threatened miscarriage and cerclage groups). All failed IUPs in the missed/incomplete group were subsequently evacuated spontaneously or actively with the aid of uterotonics, with or without a D&C. Exclusion criteria were as follows: 1) In the missed/incomplete and D&C groups, cases were excluded from analysis if the histopathologic report did not confirm the presence of an intrauterine embryonic/fetal tissue (e.g., anembryonic pregnancy, complete mole); and 2) in the threatened miscarriage and cerclage groups, cases were excluded if fetal cardiac activity was not documented after the collection of the maternal (venous) and vaginal blood specimens. No solid tissue specimens were obtained or sent to pathology from women assigned to the threatened miscarriage and cerclage groups.

In each group, AFP concentration in the vaginal blood (missed/incomplete, threatened miscarriage, and cerclage groups) or in the liquid component of the evacuated POC (D&C group) was compared with the AFP concentration in the maternal serum of the same patient. Values were expressed as median (range). Wilcoxon signed-rank test was used for paired samples. Concentration ratios were calculated for each woman individually as follows: $[AFP]_{vaginal\ blood}/[AFP]_{maternal\ serum}$ (for women in the missed/incomplete, threatened miscarriage, and cerclage groups); and $[AFP]_{POC}/[AFP]_{maternal\ serum}$ (for women in the D&C group). Receiver operating characteristic (ROC) analysis for the detection of fetal tissue in the vaginal blood according to AFP concentration ratios was performed (missed/incomplete vs. threatened miscarriage groups).

We assumed that AFP concentration in the fetal serum is $\geq$1,000 times higher than in the maternal serum (5). Because this resulted in an extremely large difference and tiny sample size, we chose to limit the effect size to 0.8, resulting in minimum of 12 patients per group (missed/incomplete vs. threatened miscarriage groups) for 80% power, with alpha = 0.05 (online sample size calculator: www.anzmtg.org/stats). Statistical data were analyzed and graphic illustrations constructed with the use of Medcalc software.

RESULTS

A total of 78 women were recruited (a greater number than the minimal power analysis requirement). After recruitment and initial evaluation (which included history taking, physical examination, sonographic imaging, and laboratory testing), each patient was assigned to one of the four groups described above; 31, 15, 9, and 23 women were assigned to the missed/incomplete, threatened miscarriage, cerclage, and D&C groups, respectively. In the cerclage group McDonald (n = 4) or modified Shirodkar (n = 5) techniques were used. Except for two women, all histopathologic reports retrospectively confirmed the presence of an IUP with embryonic/fetal tissue in the women in the missed/incomplete and D&C groups. One

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