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Original Research Article

Serum biomarkers may help predict successful misoprostol management of early pregnancy failure

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ABSTRACT

In order to simplify management of early pregnancy loss, our goal was to elucidate predictors of successful medical management of miscarriage with a single dose of misoprostol. In this secondary analysis of data from a multicenter randomized controlled trial, candidate biomarkers were compared between 49 women with missed abortion who succeeded in passing their pregnancy with a single dose of misoprostol and 46 women who did not pass their pregnancy with a misoprostol single dose. We computed the precision of trophoblastic protein and hormone concentrations to discriminate between women who succeed or fail single dose misoprostol management. We also included demographic factors in our analyses. We found overlap in the concentrations of the individual markers between women who succeeded and failed single-dose misoprostol. However, hCG levels ≥4000 mIU/mL and ADAM-12 levels ≥2500 pg/mL were independently associated with complete uterine expulsion after one dose of misoprostol in our population. A multivariable logistic model for success included non-Hispanic ethnicity and parity <2 in addition to hCG ≥4000 mIU/mL and ADAM-12 ≥2500 pg/mL and had an area under the receiver operating characteristic (ROC) of 0.81 (95% confidence interval: 72–90%). Categorizing women with a predicted probability of ≥0.65 resulted in a sensitivity of 75.0%, specificity 77.1% and positive predictive value of 81.8%. While preliminary, our data suggest that serum biomarkers, especially when combined with demographic characteristics, may be helpful in guiding patient decision-making regarding the management of early pregnancy failure (EPF). Further study is warranted.

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1. Introduction

Misoprostol is a safe, convenient, and acceptable medication for the treatment of early pregnancy failure (EPF; pregnancy failure in the first trimester), but complete uterine evacuation is only achieved in 71% of women after a single dose of 800 μg vaginal misoprostol [1]. While surgical management (uterine aspiration) is more efficacious (98–99% success [1]), non-surgical options are important to improve access and individualize patient care. EPF is often classified as anembryonic gestation and embryonic/fetal demise and incomplete/inevitable abortion. Established predictors of success and failure among those women who use misoprostol include a greater success rate with incomplete/inevitable abortion when compared with missed abortion [1–4].

The current standard of care for misoprostol management of EPF was established by a landmark randomized controlled trial [1]. Success rates among the population in this study were 71% after one dose of misoprostol, and 84% (95% confidence interval [CI] 81%, 87%) after a second dose given three days later [1]. Studies show that misoprostol is highly effective for incomplete/inevitable abortion (≥90%) [5–8], but much less effective for anembryonic gestation and embryonic/fetal demise. Morbidity and cost could be decreased if we could better predict which women with missed abortion are likely to have a successful uterine evacuation with one dose of misoprostol [9,10]. Proteins that are derived from the trophoblast and secreted into maternal circulation are differentially expressed in ectopic as compared with intrauterine pregnancies [11,12]. These proteins and others are candidate biomarkers to distinguish between the pregnancies that may be more ''resistant'' to expulsion and those that will be expelled with one dose of misoprostol. The proteins and hormones we chose to investigate are some of the many makers of the ''invasiveness'' of trophoblastic tissue. Most women undergo phlebotomy as a part of their work up for EPF, so additional testing is feasible if it would help triage women toward a management strategy with better outcomes. In this study, we tested the hypothesis that levels of trophoblast-derived proteins could identify women who achieved uterine expulsion with one misoprostol dose from those who did not successfully expel the products of conception with one dose. We also examine clinical and demographic characteristics associated with expulsion to single-dose misoprostol in our population.

2. Materials and methods

Our study was approved by the University of Pennsylvania Institutional Review Board. We conducted a sub-analysis of the data and serum collected in the misoprostol for the management of early pregnancy failure (MEPF). The MEPF study [1] was a randomized, controlled, multicenter trial that tested the efficacy, safety and acceptability of misoprostol versus surgical management in treating early pregnancy failure. The study was a multicenter trial conducted from 2002 to 2004 where participating medical centers included the University of Pennsylvania, University of Pittsburgh, Columbia University and the University of Miami. The results of the primary study have been published. Briefly, in the MEPF trial, women presenting with first trimester pregnancy failure (anembryonic pregnancy, embryonic demise, incomplete abortion and inevitable abortion) were randomized to medication uterine evacuation with an 800 μg dose of vaginal misoprostol or surgical uterine evacuation with vacuum aspiration. The medication-treated patients received four 200 μg tablets of misoprostol (Cytotec) into the posterior fornix of the vagina on day 1. They returned on day 3, and if sonographic evaluation demonstrated incomplete expulsion of products of conception, participants were given a second 800 μg vaginal dose of misoprostol and then returned on day 8 of the study for another evaluation. If the sonographic and clinical evaluation were consistent with complete expulsion of the products of conception at that time, women were contacted at 30 days for a final evaluation.

Serum samples from participants at all sites had been stored at the University of Pennsylvania at −62.2 °C. For the analysis presented here, we included all participants for whom complete records could be obtained from the MEPF database, and if there was sufficient residual banked serum to run analyses quantifying trophoblastic proteins including (vide infra). We included women who presented with anembryonic pregnancy or embryonic/fetal demise, and who had been randomized to misoprostol treatment. We excluded participants who presented with incomplete or inevitable abortion because misoprostol is highly effective for those diagnoses [9–11].

The MEPF study database was used to collect patient demographics, pregnancy-failure type, obstetrical history, clinical symptoms, and beta-hCG levels collected on days 1, 3, 8, and 15 of the original trial. In addition to hCG, the candidate markers we chose were selected based upon a thorough literature review. We chose proteins and hormones that are involved with the implantation process either from the maternal side or the pregnancy itself. Assays were conducted in the Basic Science Research Building at the Perelman school of Medicine. The following laboratory analyses were used to measure trophoblastic protein and pregnancy hormone levels in maternal sera:

- activin A (UCN Life Science Inc., Wuhan, China) was assayed using Quantikine Immunoassay kits. The minimum detectable limit for activin A was 1.25 mg/dL;
- ADAM-12 (Antibodiesonline, US Biologicals, Salem, MA, USA) protein was assayed using disintegrin and metalloprotease 12 (ADAM-12) ELISA kits. The minimum detectable limit for ADAM-12 was 24 pg/mL;
- human placental lactogen (HPL; ALPCO, Salem, NH, USA) was assayed using HPL ELISA kits. The minimum detectable limit for HPL was 1.25 mg/L;
- glycodelin (Cosmo Bio, Carlsbad, CA, USA) were assayed using Cusabio glycodelin ELISA kits. The minimum detectable limit for glycodelin was 0.78 ng/mL;
- progesterone (P4) and estradiol (E2) were analyzed using the Siemens Immulite 2000 by solid-phase, competitive binding chemiluminescent enzyme immunoassays (Siemens, Munich, Germany). The minimum detectable limits for P4 and E2 were 0.1 ng/mL and 15 pg/mL, respectively.