Optimization of third-stage management after second-trimester medical pregancy termination

Jan E. Dickinson, MD; Dorota A. Doherty, PhD

OBJECTIVE: Comparison of 3 regimens for third-stage management after second-trimester intravaginal misoprostol termination.

STUDY DESIGN: Prospective randomized trial. Three third-stage management strategies were compared: 10 units of intramuscular oxytocin (group 1), 600 μg oral misoprostol (group 2), or no additional medication (group 3) after fetal expulsion. Primary study outcome was the incidence of placental retention.

RESULTS: Two hundred fifty-one women were randomly assigned to the groups. There was a significant difference in placental retention rates: group 1, 8 of 83 (10%) vs group 2, 24 of 83 (29%) vs group 3, 26 of 85 (31%); $P = .002$. Blood loss was significantly lower in group 1, 100 mL (interquartile ranges, 50-200) vs group 2, 200 mL (interquartile ranges, 100-370) vs group 3, 200 mL (interquartile ranges, 100-375); $P < .001$. Requirment for blood transfusion: group 1, 1 of 83 (1%) vs group 2, 1 of 83 (1%) vs group 3, 5 of 85 (6%); $P = .103$.

CONCLUSION: Intramuscular oxytocin administered after fetal delivery after second-trimester medical termination significantly increases placental expulsion rates and decreases short-term postpartum blood loss.

Key words: medical termination, misoprostol, placenta, third stage

Cite this article as: Dickinson JE, Doherty DA. Optimization of third-stage management after second-trimester medical pregancy termination. Am J Obstet Gynecol 2009;201:303.e1-7.

The use of prostaglandins is established as a technique for second-trimester pregnancy termination, particularly in circumstances of fetal abnormality in which pathology review of the fetus may be required. There are many publications on routes of administration and dosage regimens for prostaglandins, either alone or after priming with mifepristone.[1-5] Less well studied are the maternal complications after second-trimester prostaglandin termination.[6] Complications of the third stage of labor, such as hemorrhage and placental retention requiring surgical evacuation, have received little research attention, despite placental surgical evacuation rates of 30-40% being reported.[3,7] Placental retention may be associated with increased blood loss, increased requirement for blood transfusion, anesthetic and operative complications, and infectious morbidity.

The high incidence of placental retention, either complete or incomplete, after second-trimester medical pregnancy termination is an area of clinical concern. Scrutiny of published termination regimens reveals a wide variation in practices between units, although there have been few formal studies on the management of the third stage in medical abortion published.[8,9] Placental retention rates vary from 8-80%,[3,7,10-12] with significant heterogeneity in uterotonic administration and permissible duration for the third stage.

The aim of this study was to compare the efficacy of 3 regimens for the management of placental delivery in second-trimester medical termination of pregnancy. Our primary intention was to develop a third-stage management protocol that minimized the incidence of placental retention and associated complications, such as hemorrhage and the need for blood transfusion.

Materials and Methods

This study was conducted as a randomized clinical trial. The investigational protocol was approved by the Institutional Ethics Committee before commencement of the study.

Women admitted to King Edward Memorial Hospital for Women, Perth, Western Australia, for second-trimester pregnancy interruption for fetal abnormality or maternal medical complication at 14-24 weeks' gestation between January 2005 and December 2007 were invited to participate in the study. Gestational age was assigned on the basis of certain menstrual dates with confirmatory ultrasound, or ultrasound dating if the menstrual dates were uncertain or varied significantly from the menstrual dates. All pregnancy terminations were performed with a standard regimen of intravaginal misoprostol administered as 400 μg every 6 hours for a maximum of 48 hours. Women undelivered after 48 hours received a transcervical Foley catheter with 2 hourly extraamniotic prostaglandin F2α (PGF2α) instillation, or high concentration intravenous oxytocin, depending on their cervical status and amniotic membrane integrity. Analgesia was provided on patient request by intramuscular meperidine (2 mg/kg maternal weight), with metoclopramide 10 mg intramuscularly as the standard antiemetic medication.

Once informed consent was obtained, the women were randomly assigned to 1 of 3 study protocols from a series of opaque envelopes prepared by using random number tables. Women allo-

From the School of Women's and Infants' Health, The University of Western Australia, and The Women and Infants' Research Foundation, Perth, Western Australia.

Presented at the 29th Annual Meeting of the Society for Maternal-Fetal Medicine, San Diego, CA, Jan. 26-31, 2009.

Received Dec. 24, 2008; revised April 26, 2009; accepted May 22, 2009.

Reprints not available from the authors.

0002-9378/$36.00

doi: 10.1016/j.ajog.2009.05.044

cated to group 1 received 10 units of oxytocin intramuscularly into the upper thigh after the fetus was expelled. Women randomly assigned to group 2 received a single oral dose of 600 μg of misoprostol after fetal expulsion. Those women allocated to group 3 received no routine pharmacologic intervention after delivery of the fetus. Because of the nature of the study protocol, it was not practical to blind the women and staff to the randomization allocation.

Routine placental curettage was not used in this trial. Spontaneous expulsion of the placenta within 60 minutes of delivery was awaited, with digital exploration of the uterine cavity and blunt curettage reserved for those cases in which expulsion did not occur or was incomplete on the basis of clinical signs and symptoms. Maternal expulsive efforts or digital extraction were permitted if the placenta had descended into the vagina. The selection of 60 minutes as the permitted duration for spontaneous placental expulsion was based on our observations over a decade.[7] In our clinical experience, if the placenta had not delivered by 60 minutes the likelihood for spontaneous passage was low (<20%).

Maternal pulse, blood pressure, and temperature were recorded every 15 minutes from fetal expulsion until placental delivery. Maternal symptoms of nausea, headache, and abdominal pain were recorded every 15 minutes on a visual analogue scale from fetal expulsion until placental delivery or transfer to the operating room. Maternal blood loss was assessed clinically by the ward and operating room nursing staff. A full blood count was performed before the commencement of the termination process and within 24 hours of placental delivery for all women.

The primary outcome measure was the incidence of failure of placental expulsion within 60 minutes of fetal delivery and the requirement for manual removal of the placenta, with the rates of placental retention compared among the 3 study arms. It was expected from our previous studies[4,7,11] that at least 40% of women would require operative delivery of the placenta when allocated to group 3, our standard regimen before this study. We planned that up to 300 women would be recruited to the study (100 per group). This sample size would achieve 80% power at a 5% significance level to detect a reduction from 40% placental retention rate on our current regimen of nonpharmacologic third-stage management to 20% placental retention either using 10 units of oxytocin after delivery or 600 μg misoprostol orally. An interim analysis was planned after 240 women had been recruited. This sufficiently large sample size at interim analysis was chosen to maximize the possibility of early stopping of the trial, if a superiority of 1 treatment was evident. The planned interim analysis was not performed because the study ceased with the introduction of mifepristone to our institution in January 2008. The introduction of mifepristone was viewed as a significant confounding factor to the conduct of the study, because of its prostaglandin augmentation effect on the uterus and the requirement to significantly alter the misoprostol protocol. Because the interim analysis was not performed, the study analysis was conducted as a single-stage analysis at the overall statistical significance of 5% for group comparisons.

Descriptive statistics used means and standard deviations (SD) (or medians and interquartile ranges [IQR]) for continuous data and frequency distributions for categorical data. The primary endpoint was evaluated by using the χ^2 test to compare the rates of placental retention among the 3 groups. Adjusted comparisons among groups were performed by using multivariable logistic regression modeling to investigate other patient characteristics that are relevant for prediction of placental retention. All tests were 2-sided and P values less than .05 were considered statistically significant. SPSS statistical analysis (version 15.0; SPSS, Inc, Chicago, IL) software was used for data analysis.

Results

Two-hundred fifty-one women were recruited to the study. Eighty-three women were randomly assigned to group 1, 83 women to group 2, and 85 received the group 3 protocol (Figure 1). No significant difference in maternal age, race, or prior uterine surgery among the 3 groups was present after randomization (Table 1). For all groups, the mean gestational age at recruitment was approximately 19 weeks (Table 1). There was no case of uterine scar rupture or hysterectomy in this study.

There was a significant difference in the rate of placental retention among the 3 groups, with those women randomly assigned to the group 1 protocol having a significantly lower rate of placental retention than those in groups 2 and 3 (Table 2). Compared with a protocol of no pharmacologic intervention (group 3), logistic regression analysis showed the administration of intramuscular oxytocin (group 1) was associated with a significantly lower rate of placental retention (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.1–0.57; P = .001). The misoprostol regimen (group 2) was associated with a placental retention rate similar to that of the no-pharmacologic intervention group (OR, 0.92; 95% CI, 0.47–1.79; P = .813) (Figure 2).

In this study with a policy of planned operative removal of the placenta if expulsion had not occurred after 60 minutes, the third-stage duration range was broad (1-455 minutes), with delays principally because of the difficulty in accessing the operating room facilities at night. Review of the survival curves for placental delivery in the 3 groups demonstrates that after 120 minutes, the chance of nonoperative placental expulsion is extremely low (Figure 3). For women with a third-stage duration of 60-120 minutes, 67.3% (37/55) required operative removal with 32.7% (18/55) delivering before reaching the operating room. For women with a third stage of 120-455 minutes, only 1 woman delivered the placenta before operative intervention, 97.3% (36/37) requiring manual removal.

There was an inverse relationship between gestation at termination and placental retention. Increasing gestation was associated with a reduction in the incidence of placental retention (P = .01) and this effect was similar in all 3 groups (P = .821). There was no effect of parity