Misoprostol and active management of the third stage of labor

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**SPECIAL ARTICLE**

**KEYWORDS**
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Misoprostol;
Active management of the third stage of labor

**Abstract**

**Objective:** To compare current practices for the active management of the third stage of labor (AMTSL) with the use of 600 \( \mu \)g of oral misoprostol. **Methods:** An operations research study was designed to compare blood loss with current AMTSL practices and misoprostol use. **Results:** Women in the misoprostol group were less likely to bleed 500 ml or more (adjusted odds ratio, 0.30; 95% confidence interval, 0.16–0.56) compared with those in the current practices group. In the current practices group 73% women required interventions because of postpartum hemorrhage, compared with 11% in the misoprostol group. **Conclusion:** In situations where oxytocin and or ergometrine are not consistently and appropriately used during third stage of labor, misoprostol should be considered for inclusion in the AMTSL protocol.

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1. Introduction

In Egypt, although the maternal mortality ratio decreased from 174 to 84 per 100,000 live births between 1992–1993 and 2000, for a 52% reduction, the distribution of causes of death has not changed [1]. According to the National Maternal Mortality Study conducted in Egypt in 2000, postpartum hemorrhage (PPH) alone was responsible for 27%
of all maternal deaths, making it the leading contributor to maternal mortality in that country.

Routine active management of the third stage of labor (AMTSL) has been recommended for vaginal deliveries in hospital settings [2,3]. It involves prophylactic administration of uterotonics before delivery of the placenta, early cord clamping and cutting, and controlled umbilical cord traction. Recommended uterotonics are oxytocin (10 IU administered intramuscularly or intravenously or an infusion of 20 IU intravenously) or ergometrine (0.2 mg intramuscularly or intravenously) [4]. In contrast, in expectant management of the third stage of labor, placental delivery is spontaneous or aided by gravity or nipple stimulation—without the use of uterotonics.

In Egypt, the most recent essential obstetric care protocol for physicians, published by the Ministry of Health and Population, describes both active and expectant management of the third stage of labor [5]. For active management, the recommended uterotonic drug is oxytocin (5 IU) administered intramuscularly at the time of the delivery of the anterior shoulder. The protocol suggests that oral tablets of ergometrine have little effect on postpartum blood loss. Controlled cord traction, i.e., traction on the cord combined with upward counterpressure applied to the lower segment of the uterus, is recommended by the protocol to reduce blood loss and shorten the third stage of labor. However, the protocol does not encourage cord clamping immediately after delivery because of the perceived small effect on the incidence of PPH, and it may deprive the newborn of needed hemoglobin.

Misoprostol, an E1 prostaglandin analogue, is a potent uterotonic agent whose usefulness is increasingly recognized in obstetric and gynecologic practice, including in the control of PPH [6–8]. Misoprostol can be administered orally, rectally, vaginally, or sublingually without syringes or intravenous equipment, and it is inexpensive, easy to store and stable at room temperature [9]. Studies comparing the results of prophylactic use of misoprostol for the reduction of blood loss with conventional uterotonics have concluded that misoprostol had a positive effect [10–21]. Although some studies have found that conventional uterotonics were superior to misoprostol, none has rejected using misoprostol when injectable uterotonics are not available or cannot be properly used [22,23]. Moreover, the 2003 conference on underused technology to reduce maternal mortality organized by Parkway Academy of Technology and Health in Bellagio, Italy, called for a greater interest in the role of misoprostol in AMTSL [24].

A careful analysis of the management of the third stage of labor in an Egyptian teaching hospital showed that only 15% of the women received adequate AMTSL during the study period [25]. Staff shortages were given as the main explanation for the generally inappropriate management of deliveries, and that study’s findings are not unique. It is in these widespread circumstances that, given its ease of administration, misoprostol may have an advantage over conventional, intramuscularly or intravenously delivered uterotonics.

An operations research study was conducted at three Egyptian hospitals to compare current AMTSL practices with the use of 600 μg of oral misoprostol as the uterotonic agent.

2. Methods

Menya University Hospital, Assiut University Hospital and Benha University Hospital were involved in the study over a period of 6 months. Together, these 3 hospitals employ 73 obstetricians, perform on average 700 deliveries per month, and have a maternal mortality ratio of 363 per 100,000 live births. According to hospital records, about 38% of maternal deaths are due to PPH and the incidence of PPH is about 5%.

At each study site, the research period was divided into two phases, a pre-intervention phase that occupied the first 3 months and an intervention phase that lasted through the last 3 months of the study.

During the pre-intervention phase, trained staff at the participating hospitals obtained informed consent from women admitted for delivery (inclusion criteria were anticipated vaginal delivery, gestational age > 36 weeks and ability to give informed consent) and collected blood for antepartum estimation of hemoglobin concentration. Women were excluded if they had bronchial asthma, other chronic disease (e.g., heart disease and/or diabetes), or any condition that could put them at higher risk for poor delivery outcomes if they participated in the study.

After delivery and clamping of the umbilical cord, a calibrated drape was placed under the women’s buttocks for blood loss measurement. The calibrated drape remained in place for approximately 4 h following delivery, and blood loss was read cumulatively every 20 min. Antepartum, delivery and postpartum care were given to all women according to standard practices at the university hospitals. Postpartum hemoglobin concentration was assessed in women who needed to be hospitalized for more than 24 h because of PPH.
During the pre-intervention phase, apart from the use of the drape for blood loss collection, physicians continued to use the current AMTSL practices. In the intervention phase, all AMTSL procedures were still encouraged but the only uterotonic agent used prophylactically was misoprostol (600 µg orally).

The same data collection instrument was used at the three sites, and the data recording was done in stages (upon admission, soon after delivery, every 20 min after delivery for up to 4 h, and before discharge) by a physician trained as a clinical research officer. Data collected from each participant included sociodemographic characteristics, medical and obstetric history, assessment of blood loss every 20 min for the first 4 h after delivery, adverse effects of the intervention, any medication or other intervention received by the participant between admission and discharge, and condition of the newborn. The Egyptian ethics committee approved the study protocol, and the Healthy Mother Healthy Child Project, implemented in Egypt by John Snow Inc. under United States Agency for International Development (USAID) Contract No. 263-C-00-98-0041-00, was responsible for study implementation. The misoprostol used (Misotec; Sigma Co., Moubarak Industrial City, First Quarter Quesna, Egypt) was donated by Ventures Strategies for Health and Development.

The database was developed using the Epi Info software system, version 2002 (available from the Centers for Disease Control and World Health Organization), and statistical analysis was performed using the Stata Statistical Software, release 8.0 (College Station, Tex, USA). Descriptive statistics were reported and the main outcomes estimated and compared between the two study phases. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the main study outcomes. Adjusted ORs were estimated using a logistic regression model and corresponding \( P \) values (two-sided maximum likelihood test). Mean blood loss at 20, 40, 60, 80, 100 and 120 min) and 95% CIs were estimated and compared between study phases. Participants who were enrolled but then had a cesarean section or an instrument-assisted delivery were excluded from the final comparison analysis.

### 3. Results

A total of 2532 women were enrolled in the study, 53% of whom during the pre-intervention phase. The participants’ sociodemographic as well as pregnancy and medical history characteristics are shown in Table 1. A majority of women (69%) were aged between 20 and 29 years, with no significant difference between the study phases, and 46% were illiterate, with similar distributions in the pre-intervention (45%) and intervention (47%) phases. Furthermore, the participants’ parity was similar in the two study phases.

The pregnancy and medical histories taken upon admission showed the similarity of the study populations in the two phases. Most women had at least one antenatal visit. Hemoglobin levels were assessed for only 1807 women, 57% of whom from the pre-intervention phase. Less than 1% of women in either study phase had experienced previous PPH and retained placenta (data not shown).

The pre-intervention phase consisted in collecting information from current practices in the management of the third stage of labor. During this phase, 7% of the participants received no uterotonic agent, and the remaining 93% received either oxytocin or ergometrine (Table 2). Of those receiving oxytocin \( (n=609) \), about 35% received 5 IU and the remaining received 10 IU or more. Of those receiving ergometrine \( (n=621) \), about half re-
received 0.4 mg and the remaining received 0.2 mg. The route of administration for ergometrine was intramuscular; for oxytocin, it was intramuscular for those receiving 5 IU and intravenous for those receiving 10 IU or more. During the intervention phase, all participants received 600 μg of misoprostol orally. Unlike the administration of uterotonics, which was not universal, uterine massage, cord traction and early cord clamping were performed in almost all cases regardless of the study phase.

The cumulative mean blood loss during each study phase and respective 95% CIs around the mean are presented in Fig. 1. On average, women enrolled during the intervention phase and receiving misoprostol as part of AMTSL lost less blood than those enrolled during the pre-intervention phase. Fig. 1 also shows that, for each time point after delivery, the mean blood loss was significantly lower in the intervention (misoprostol) than in the pre-intervention (current AMTSL practices) phase.

Statistically significant differences were observed between the pre-intervention and the intervention groups regarding the amount of blood loss at the two most important cut-off points for vaginal bleeding after delivery (Table 3). Results show that, when the blood loss was 500 ml or greater, women in the misoprostol group were less likely to incur PPH (adjusted OR, 0.30; 95% CI, 0.16–0.56). The difference between the two groups was even more pronounced for severe PPH (adjusted OR, 0.12; 95% CI, 0.02–0.93).

Additional uterotonic agents were given to 73% of the women who experienced PPH in the pre-intervention phase, compared with only 11% in the intervention group. Of the main potentially adverse effects measured 20 min after delivery, women in the intervention group were consistently more likely to develop high temperature (≥37 °C), shivering, nausea and vomiting (Table 3). The mean temperature of the participants was 37.1 °C in the pre-intervention group and 37.3 °C in the intervention group, and less than 1% of the participants needed to be treated for pyrexia. Although nausea and vomiting affected only a small number of participants, the number was significantly higher in the intervention group.

A separate analysis that excluded the women who did not receive uterotonics in the pre-intervention phase was performed for the main study outcomes and a slightly but significantly lower adjusted OR was found (0.36 vs. 0.30). The same was found regarding the need for additional interventions. Without the women who did not receive uterotonics, the adjusted OR for a blood loss of 1000 ml or greater was insignificant.

### 4. Discussion

This study was intended to provide information for the review and possible revision of the current Ministry of Health and Population policy in Egypt on the management of the third stage of labor. It can

### Table 2 History of third stage of labor among women with vaginal deliveries

<table>
<thead>
<tr>
<th></th>
<th>Pre-intervention</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early cord clamping</td>
<td>96.9</td>
<td>99.2</td>
</tr>
<tr>
<td>Cord traction</td>
<td>98.4</td>
<td>99.4</td>
</tr>
<tr>
<td>Uterine stage</td>
<td>97.2</td>
<td>99.1</td>
</tr>
<tr>
<td>Use of uterotonics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>7.2</td>
<td>n/a</td>
</tr>
<tr>
<td>Oxytocin or ergometrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>n/a</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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**Figure 1** Cumulative mean blood loss and 95% confidence intervals according to study period (vaginal deliveries).
also help inform policy makers on the feasibility of using misoprostol in AMTSL, especially in resource-poor settings where other uterotonic are unavailable or wherever AMTSL is not practiced. In recent years, an increasing body of literature has shown the importance of using uterotonic in AMTSL, and many international organizations, including FIGO, recommend that uterotonic be used in all deliveries to decrease PPH-associated morbidity and mortality. In Egypt, despite the success achieved in overall reduction of maternal mortality in the last decade, PPH continues to be the single most important cause of maternal mortality.

The study sites chosen for this operations research study are university hospitals similar in availability of staff, client volume and maternal and neonatal outcomes, with similar experience conducting operations research study in the labor ward. The study was designed as a quasi experiment, where the study factor was assessed and compared between two groups without the use of randomization. These types of studies have limitations. They do not test for the efficacy of a therapeutic or prevention measure; they can introduce bias due to greater attention from the care provider during the intervention phase; and the lack of randomization can introduce distortions in the results. However, the efficacy of misoprostol has been well established in other studies, some of them reviewed in the present article, and the superiority of conventional uterotonic is not been questioned in this study. The major contribution of this type of design, as in the present study, is to evaluate the effectiveness of a planned intervention and suggest program and policy changes in response to this evaluation.

Results from this study demonstrate that in a busy hospital misoprostol can offer the optimum care at delivery. These findings are in contrast to those reported by Gulmezoglu et al. [22]. Theirs was a randomized controlled experiment (oxytocin vs. misoprostol), whereas the present study simply standardized the “treatment effect” with misoprostol while maintaining real-life labor ward conditions. The main goal of this operations research study was not to assess the efficacy of uterotonic, but to assess the effectiveness of implementing a standardized, easy to manage intervention during the third stage of labor. The similarity in the participants’ characteristics in the pre-intervention and intervention phases is reassuring, and the women enrolled in both study periods would have had a similar likelihood of experiencing PPH.

This study’s findings about the quality of management of the third stage of labor, particularly during the pre-intervention phase, are in agreement with what was found by Cherine et al. [25]. Day-to-day practice in delivery rooms can be inconsistent, especially when uterotonic are used. Dosages are not standardized and in some cases uterotonic are not used. Regarding blood loss, the observed differences were unexpectedly great, which suggests that careful attention should be paid to the chemical stability of ergometrine and oxytocin. Available studies on delivery-related blood loss do not address this issue and the present study cannot address it. Moreover, the great variation in doses and routes of administration of uterotonic could have affected what constitutes AMTSL. The difference in the mean blood loss 20 min after delivery is also surprising, given that the intramuscular and intravenous routes are expected to cause contractions earlier than the oral route, and therefore to result in less blood loss. However, it is difficult to assess how different the present study population may be from other

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**Table 3** Primary and secondary study outcomes among women with vaginal deliveries

<table>
<thead>
<tr>
<th></th>
<th>Pre-intervention (current practice)</th>
<th>Intervention (misoprostol)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss=500 ml</td>
<td>73/1324 (5.5%)</td>
<td>19/1178 (1.6%)</td>
<td>0.28* (0.17 to 0.47)</td>
<td>0.30* (0.16 to 0.56)</td>
</tr>
<tr>
<td>Blood loss=1000 ml</td>
<td>11/1324 (0.8%)</td>
<td>1/1178 (0.1%)</td>
<td>0.10** (0.01 to 0.79)</td>
<td>0.12** (0.02 to 0.93)</td>
</tr>
<tr>
<td>Additional interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among those PPH</td>
<td>53/73 (72.6%)</td>
<td>2/19 (10.5%)</td>
<td>1.04** (0.01 to 0.27)</td>
<td>0.02** (0.00 to 0.19)</td>
</tr>
<tr>
<td>Among study participants</td>
<td>53/1324 (4.0%)</td>
<td>2/1178 (0.2%)</td>
<td>0.04** (0.01 to 0.17)</td>
<td>0.03** (0.00 to 0.19)</td>
</tr>
<tr>
<td>Main side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temp.&gt;37 °C</td>
<td>169/1324 (12.7%)</td>
<td>280/1178 (23.0%)</td>
<td>2.80* (2.16 to 3.53)</td>
<td>1.63** (1.20 to 2.20)</td>
</tr>
<tr>
<td>Shivering</td>
<td>79/1297 (6.1%)</td>
<td>253/1119 (22.6%)</td>
<td>4.50* (3.45 to 5.89)</td>
<td>4.03* (2.93 to 5.55)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30/1295 (2.3%)</td>
<td>73/1119 (6.5%)</td>
<td>2.90* (1.90 to 4.50)</td>
<td>3.74* (2.33 to 6.00)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17/1295 (2.3%)</td>
<td>39/1115 (3.5%)</td>
<td>2.70** (1.50 to 4.80)</td>
<td>3.36* (1.81 to 6.22)</td>
</tr>
</tbody>
</table>

*p<0.05; **Fisher’s exact test.

a Adjusted for parity, integrity of membranes, antenatal Hgb and time from admission to birth. Additional interventions among those with PPH are adjusted for parity, integrity of membranes and time from admission to birth.
study populations. To date, there are no available published results of blood loss in the first 20 min after prophylactic use of uterotonics. Studies tend to report total blood loss using cut-off points (i.e., 500, 750 and 1000 ml).

There exists a possibility of bias among health care providers, who might have paid greater attention in the intervention phase, but it cannot be the only reason for the differences between the two groups. Other components of active management (uterine massage, cord traction and early clamping) were almost universally administered and not significantly different between the two study phases. Furthermore, the analysis of the study population without the women who did not receive uterotonics showed significant differences between the two groups, and these differences were in favor of the intervention. There was no significant difference when severe blood loss (≥1000 ml) only was considered, but this can be attributed to the fact that severe PPH occurred in less than 1% of the participants.

It is clear from the results that 600 µg of oral misoprostol can reduce total blood loss after delivery. The advantage of using misoprostol is its easy administration, and also the fact that only one drug regimen is used. The downside of this potent uterotic is that women taking misoprostol are at higher risk for a higher temperature, shivering, nausea and vomiting. However, none of these effects are life-threatening; a very small proportion of women require treatment to alleviate them; and these effects can be easily managed by delivery room staff. In summary, the benefits from a substantial decrease in the number of women that will develop PPH and in need of additional uterotonics, outweigh the risks of side effects associated with misoprostol.

In conclusion, misoprostol is a proven, potent uterotic agent. In situations where oxytocin and or ergometrine are not consistently and appropriately used for active management of the third stage of labor for various reasons (i.e. drug shortage, shortage of staff to administer i.v./i.m., storage and or refrigeration problems, high case-load, etc.), misoprostol should be considered for inclusion in the protocol for AMTLS.

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