# Rectal Misoprostol in Management of Retained Placenta: A Contradictory Result

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***Background:*** *Retained placenta is one of the common problems in obstetric practice. The most common procedure to manage cases with retained placenta is manual removal of placenta (MROP) under general anesthesia. Recent data indicates that misoprostol may be helpful in decreasing the rate of MROP.*
***Objective:*** *To assess the efficacy of rectal misoprostol in women with delayed placental separation.*
***Material and Method:*** *A descriptive, retrospective cohort was conducted. All pregnant women with retained placenta longer than 30 minutes after fetal delivery, either in second or third trimester that received 800 mcg rectal misoprostol were included in the present study. Successful treatment was defined as spontaneous placental expulsion within 30 minutes after rectal misoprostol administration.*
***Results:*** *The rate of spontaneous placental expulsion within 30 minutes after misoprostol administration was very low, only three out of 20 cases (15%).*
***Conclusion:*** *High dose rectal misoprostol does not give a promising result in cases of retained placenta. It is ineffective to facilitate placental separation in cases of retained placenta and does not seem to decrease the rate of MROP.*

***Keywords:*** *Misoprostol, Retained placenta, Manual removal of placenta*

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Retained placenta is one of the common complications in obstetric practice. The incidence is varied widely, 1%-23%[1-4], depending on the definition and characteristics of patients. Based on the authors' experience, it was found in about 10% or more[5,6] in the second trimester, higher than that in term pregnancy. The serious consequence of retained placenta is postpartum hemorrhage, which is often associated with maternal morbidity and mortality. Moreover, it is also related to an increased risk of puerperial infection. The most common practice in cases of retained placenta is manual removal of placenta (MROP). However, such a procedure needs trained personnel for both placental removal and anesthesia management. Accordingly, MROP is not very safe for patients and relatively invasive.

When should MROP be started after fetal delivery? Generally, decision making depends on many factors such as amount of bleeding, maternal vital signs, parity, and gestational age as well as attitude of the attending physicians. In uncomplicated cases, some institutes attempt MROP after 30 minutes of fetal delivery but some start at 60 minutes. Kirz[7] suggests that for second trimester pregnancy termination with PGE2, if the placenta is not spontaneously expelled after 30 minutes of fetal delivery, the rate of maternal complication will be increased. Several medical methods are proposed to manage retained placenta, including intraumbilical oxytocin, PGF2a and misoprostol. The benefit of these techniques is controversial. For example, some studies show the effectiveness of intraumbilical vein oxytocin 10 units superior to intravenous oxytocin plus 0.5 mg ergometrine[8], whereas some studies demonstrate that high dose intraumbilical vein oxytocin is not superior to placebo, in terms of shortening the third stage of labor or the need of surgical intervention for retained placenta[9].

In case of pregnancy termination in second trimester, Sundaram et al[10] reported that the use of PGF2a has been shown to have shorter third stage of labor and lower rates of retained placenta when compared to rectal misoprostol. On the contrary, Li

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et al[11,12] demonstrated that 800 mcg rectal misoprostol in cases of retained placenta is highly effective to spontaneously expel placenta within 35 minutes. None of the 18 cases in these studies needed MROP. To date, the studies on the role of misoprostol in management of retained placenta are very limited and there is no report by other groups. Therefore, the authors conducted the present study to assess the efficacy of rectal misoprostol in management of retained placenta.

**Material and Method**

A descriptive retrospective cohort study was carried out at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand. The present study was approved by the ethic committee of the Faculty of Medicine, Chiang Mai University. Pregnant women who were diagnosed for retained placenta were recruited into the present study. The inclusion criteria were 1) women giving vaginal birth in the second or third trimester, 2) spontaneous delivery of placenta did not occur within 30 minutes after fetal delivery, 3) no active vaginal bleeding over the period of 30 minutes after fetal delivery, 4) stable vital signs, and 5) no signs of placental separation. Exclusion criteria included 1) active vaginal bleeding which required surgical intervention after misoprostol administration, 2) multifetal pregnancy, 3) misoprostol hypersensitivity, and 4) subsequently proven to be placental adherens. The participants received misoprostol 800 mcg (four 200 mcg-tablet without moistening) rectally by the attending physician at 30 minutes after fetal delivery. The time of administration and placental delivery as well as vital signs and bleeding were recorded. During such a period, no other intervention to facilitate placental separation or delivery such as uterine manipulation was given. In addition, the baseline characteristics of the patients such as age, parity, gestational age, route of delivery, etc and adverse events of misoprostol were also recorded. If the placenta was not expelled within 30 minutes after misoprostol administration, these cases were defined as failure with misoprostol use. The attending physicians could manage by their own decision such as further waiting thereafter or MROP. If active bleeding occurred during the period of 30 minutes of misoprostol use, MROP or dilatation and evacuation could be done immediately. Descriptive statistics were used to summarize the data in term of frequency, percentage, range, mean $\pm$ standard deviation (SD) and median.

**Results**

During the present study, 21 women were recruited and one case was finally excluded because this patient was later diagnosed for placental adherens and ended up with hysterectomy. The remaining 20 cases were available for analysis.

The mean age of the mothers was 31.90 $\pm$ 6.32 years (21-44). The mean gestational age was 28.95 $\pm$ 9.26 weeks (19-42, the median of 28 weeks). The percentage of nulliparous women was 60.0%. Of the recruited cases, nine (45%) had spontaneous labor, eight (40%) had preinduction with misoprostol followed by oxytocin, and three (15%) were induced by oxytocin. The mean placental delivery time after misoprostol administration was 54.80 $\pm$ 35.59 min (14-180) and the median time of placental delivery after drug use was 45.50 min. Three cases (15%) had complete placental delivery within 30 minutes after misoprostol use, 14, 15 and 30 minutes respectively. All but one had placental delivery within 100 minutes.

Only one of five women with previous curettage has successful placental delivery with misoprostol use. Her placental delivery time was 14 minutes while two of them had spontaneous placental delivery at 41 minute (4 previous curettages) and 180 minute (1 previous curettage). Another two of them ended up with MROP (1 previous curettage) and evacuation and curettage (2 previous curettage).

Among the cases of no response to misoprostol (17 cases; 85%), most ended up with MROP (5 cases) and evacuation and curettage (5 cases). Seven cases (35%) delivered placenta spontaneously after 30 minutes of the study period (range 38 to 180 minutes) without any serious complication except two of them requiring light curettage due to retained pieces of placenta.

Ten cases were in second trimester and the other 10 were in third trimester (Table 1). Among cases of no intervention, the mean placental delivery of the women in the second trimester tended to be longer; 70.20 $\pm$ 43.3 vs. 39.40 $\pm$ 16.5 minutes, though not statistically significant.

During observation among the failed cases, one patient had postpartum hemorrhage, and MROP was performed. Over the period of 30 minutes of misoprostol use, there was no case of postpartum hemorrhage, defined by estimated blood loss of more than 500 ml. The rate of adverse events was very low. Fever and nausea as well as vomiting was found only in one case (5%).

**Table 1.** A comparison of baseline characteristics and outcome of the parturients in the second and third trimester

| | Second trimester (n = 10) | Third trimester (n = 10) | p-value |
|---|---|---|---|
| Age | 33.60 ± 5.6 | 30.20 ± 6.8 | >0.05 |
| Nulliparity | 60% | 60% | >0.05 |
| Mean GA (weeks) | 24.70 ± 3.16 | 37.20 ± 3.99 | <0.001 |
| Fetal weight (grams) | 718 ± 521 | 2,799 ± 578 | <0.001 |
| Placental weight (grams) | 188 ± 120 | 486 ± 211 | <0.001 |
| Success rate | 10% | 20% | >0.05 |
| Placental delivery time in cases of no intervention (min) | 70.20 ± 43.3 | 39.40 ± 16.5 | 0.05 |

GA = gestational age

## Discussion

The incidence of retained placenta depends on the set up protocol period. The shorter cut off time point for diagnosis such as 30 minutes versus 60 minutes, the more incidences will be found[1,13]. In case of no active bleeding, the authors routinely have intervention for retained placenta at 30 minutes after fetal delivery.

Retained placenta may be associated with maternal morbidity and mortality, especially in developing countries where resources for appropriate obstetrical care are limited. Conventional treatment of retained placenta is manual removal under anesthesia, which can only take place in larger health care facilities. Medical treatment of retained placenta with prostaglandins E1 (misoprostol) could be cost-effective and easy-to-use and could be a life-saving option in many low-resource settings. Based on preliminary reports by Li et al[11,12], rectal misoprostol seems to be effective to facilitate placental separation since all of 8 and 18 cases in their two separate reports had been successful with rectal misoprostol (800 mcg). Therefore, the present study describes an experience of such a treatment in cases of retained placenta in a low resource setting. Nevertheless, the present study cannot reproduce such a promising result, in spite of the same protocol as suggested by Li et al[12]. Of 20 cases in the present study, misoprostol may have been helpful in placental separation in 30 minutes of use in only 15% of cases. This seems to be a lower rate of spontaneous placental expulsion than expected. Moreover, the authors cannot conclude that the successful expulsions whether they were associated with misoprostol or spontaneous process since there was no control in the present study. The reason for the different results is unclear but this may partly be explained by too small a sample size (8 cases) in one of their reports and longer time of observation before and after misoprostol use in the other report (35-40 minutes)[11,12]. In addition, the authors included five cases (20%) with previous curettage and four of them failed to deliver placenta in 30 minutes. This may affect the lower likelihood to spontaneous expulsion of placenta. Moreover, most cases in the present study were in preterm. Incidence of retained placenta in preterm pregnancy is more often than in term pregnancy[3]. Additionally, if it is in the second trimester the placenta is expelled within two hours by only 60%[7,13].

Of interest, more than half of second trimester pregnancy received a repeated dose of misoprostol for pregnancy termination. When misoprostol is given again after fetal delivery in cases of retained placenta, it might not work very well. The repeated dose of vaginal misoprostol does not significantly increase the blood level of the active metabolite of misoprostol[11,14]. Repeated administration via rectal or vaginal form is likely to show a similar result. This may be another explanation why the present study does not show a similar result as Li's. Other reasons that were not mentioned in previous studies include uterine manipulation during observation and possibly accounting on the success rate.

Adverse effects of rectal misoprostol in the present study are very low. This might be because misoprostol in the tablet form has a lower adverse event when compared to the gel form[6].

The contradictory results concerning efficacy of misoprostol use in facilitating placental separation may be resolved by the ongoing randomized controlled trial aimed to evaluate the efficacy of 800 mcg sublingual misoprostol in term of reducing the rate of MROP compared to placebo[15]. Misoprostol in sublingual route may have a better pharmacokinetic

profile in terms of shortest onset of action, greatest peak plasma level greatest area under the curve compared to other routes of administration[14,16].

In conclusion, 800 mcg rectal misoprostol for placental separation in the cases of retained placenta is not as effective as expected. The authors cannot recommend this regimen for management of retained placenta. However, sublingual misoprostol or other regimens may be further studied to test the efficacy in all gestational ages.

**Potential conflicts of interest**

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## การใช้ rectal misoprostol ในกรณีที่รกลอกตัวช้า: ผลที่แตกต่างจากการศึกษาที่ผ่านมา

**สายพิณ พงษธา, ธีระ ทองสง**

***ภูมิหลัง**: Retained placenta เป็นปัญหาที่พบได้บ่อยมากประการหนึ่งทางสูติศาสตร์ โดยทั่วไป เมื่อพบปัญหานี้ก็ทำการล้วงรกภายใต้การดมยาสลบ ซึ่งเป็นหัตถการที่ต้องอาศัยความชำนาญ และต้องระวังภาวะแทรกซ้อนจากยาสลบด้วย ข้อมูลที่มีรายงานมาในระยะหลังชี้ว่าการใช้ rectal misoprostol มีประโยชน์ในการทำให้รกลอกตัวออกมาจึงทำให้ช่วยลดอัตราการล้วงรกลง การศึกษานี้จึงได้ดำเนินการเพื่อประเมินประสิทธิภาพของ rectal misoprostol ในกรณีที่มี retained placenta*

***วัสดุและวิธีการ**: เป็นการศึกษาเชิงพรรณนาและ retrospective cohort โดยคัดเลือกสตรีที่คลอดทารกแล้ว 30 นาที แต่ยังไม่มีการคลอดรกออกมาไม่ว่าจะเป็นสตรีที่หลังการแท้งในไตรมาสที่สองหรือสตรีที่คลอดทารกในไตรมาสที่สาม โดยทุกรายได้รับ rectal misoprostol 800 ไมโครกรัม ครั้งเดียว การแปลผลความสำเร็จจากการให้ยา คือ มีการคลอดรกออกมาได้เองภายใน 30 นาทีหลังจากได้รับยา*

***ผลการศึกษา**: การใช้ misoprostol ให้ผลสำเร็จที่ต่ำมากคือ 3 รายใน 20 ราย หรือ เท่ากับร้อยละ 15*

***สรุป**: การใช้ rectal misoprostol ขนาดสูงไม่ได้ผลดีในสตรีที่มีการลอกตัวของรกช้า และไม่ช่วยให้อัตราการล้วงรกลดต่ำลงมากซึ่งในการศึกษานี้แตกต่างจากรายงานที่ผ่านมา*