

# Which factors may influence the duration of misoprostol-induced abortion in the second trimester?

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## Summary

**Background:** To investigate the factors that may affect the time interval between induction and fetal expulsion in misoprostol-induced termination of second trimester pregnancy. **Materials and Methods:** A retrospective analysis of second-trimester pregnancies terminated in the second trimester between October 2008 and 2010 was performed. Induction was done by administration of 400 mcg intravaginal misoprostol. The correlation between the duration of abortion and maternal, fetal, and clinical features were statistically analyzed with multivariate regression analysis. **Results:** One hundred and seventy-five singleton pregnancies that met the inclusion criteria were evaluated. The average gestational age at the first induction was 18.3 weeks. The mean time interval between the first induction and expulsion was  $37.2 \pm 21.3$  (range 3 to 160) hours. Fetal expulsion occurred significantly at a later gestational age and those with a higher blood glucose level at admission. However, no correlation could be established between the duration of abortion and the number of pregnancies, deliveries, age, hemoglobin levels or platelet count. **Conclusions:** Misoprostol is safe and effective in induction of abortion during second-trimester pregnancies. The induction-to-abortion interval is longer in patients with hyperglycemia and advanced gestational age. Prospective, randomized studies are necessary to better understand the factors influencing the duration of abortion.

**Key words:** Termination of pregnancy; Mid-trimester; Abortion; Misoprostol; Duration.

## Introduction

Termination of pregnancy (TOP) is one of the most common procedures in obstetrics and gynecology. There is a rise in the first- and second-trimester abortions due to the detection of chromosomal abnormalities and major structural fetal malformations by antenatal screening programs [1, 2]. Termination can be performed either by surgical evacuation or medically by prostaglandins. In general, prostaglandins have been reported to be safe and efficient for the induction of labor and termination of pregnancy [3].

A prostaglandin E1 analog, misoprostol, is widely prescribed for the prevention and treatment of peptic ulcers that may result from long-term use of non-steroidal anti-inflammatory drugs. Although not registered for the induction of abortion, misoprostol has been commonly used for this purpose. Use of labor induction agents in the second trimester are indicated mostly for congenital fetal anomalies and intrauterine fetal demise. However, use of misoprostol for second-trimester TOP is reported to be associated with uterine rupture, especially when combined with intravenous oxytocin infusion [4, 5].

In particular, the time from the initiation of abortion to expulsion is hard to predict. Dickinson had suggested that gestational age, maternal age and parity were parameters that may affect this time interval in cases where vaginal misoprostol was utilized [6]. Similarly, Wagner had stated that the only relevant contributors to estimation of the time interval in this group of patients were gestational age and previous history of spontaneous delivery [1].

The aim of the present study was to analyze the factors that could possibly influence the duration of medical termination of pregnancy in the second trimester. On the basis of the existing evidence, the authors chose 400-mcg dose of misoprostol and administered it vaginally every six hours including up to four doses [4, 5].

## Materials and Methods

This retrospective study consisted of all singleton pregnancies terminated using prostaglandins between October 2008 and 2010 in the obstetrics and gynecology department of a tertiary care center. The pregnancies were terminated between 11 and 24 weeks of gestation on the basis of present or expected severe maternal distress due to fetal abnormalities. For each case, maternal and pregnancy-related features, the induction interval, clinical characteristics, and the dose of prostaglandin administered were evaluated from the hospital database. The induction interval as an outcome parameter was defined as the time interval between the first application of the prostaglandin and the end of fetal expulsion.

Pregnancies were terminated due to various major congenital anomalies or intrauterine fetal demise. Gestational week was calculated from the last menstrual period. Congenital anomalies were diagnosed by ultrasonographic examination and a written informed consent was obtained from the patients for TOP. Intrauterine fetal demise was diagnosed when no fetal cardiac function was observed during obstetric ultrasonography.

On the basis of the existing evidence, the authors chose a 400-mcg dose of misoprostol and administered it vaginally every six hours including up to four doses [6, 7]. Induction was repeated every four to six hours until relevant contractions were recorded. Patients with a history of a spontaneous delivery without previous cesarean section had received misoprostol. Prostaglandins were inserted vaginally every four to six hours until relevant contrac-

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tions were recorded. The patients were hospitalized during the whole induction procedure.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software (version 15.0 for Windows). All differences associated with a chance probability of 0.05 or less were considered statistically significant. Multivariate regression analysis was used to evaluate the impact of variables on the duration of abortion.

## Results

Data were gathered from the medical records of 175 women with a mean age of  $27.8 \pm 6.1$  (range 16 to 47) years. The average number of previous pregnancies and deliveries were 4.4 and 2.8, respectively. The average gestational age at the first induction was 18.3 (range 15 to 26) weeks. The mean time interval between the first induction and expulsion was 37.2 (range 3 to 160) hours. Total dose of misoprostol administered varied between 400 mcg to 1,600 mcg.

Multivariate regression analysis of maternal, fetal, and clinical variables demonstrated that total dose of misoprostol ( $p < 0.001$ ), blood glucose level at admission ( $p = 0.028$ ), and gestational age ( $p = 0.001$ ) were correlated with the duration of abortion procedure. Whereas, age ( $p = 0.094$ ), number of previous pregnancies ( $p = 0.513$ ), and previous live births ( $p = 0.607$ ), hemoglobin levels ( $p = 0.074$ ) and platelet counts ( $p = 0.735$ ) did not seem to influence this time interval (Table 1).

## Discussion

TOP in the second trimester can be undertaken for various clinical indications [1]. Several methods for second-trimester abortion have been used, including hysterotomy, dilatation and curettage, hyperosmolar fluid injection into the amniotic fluid, administration of prostaglandins, oxytocin, anti-progesterone, methotrexate or a combination of these agents [2].

Misoprostol is an effective uterotonic drug commonly used for induction of abortion. Pharmacologically, the drug is a methylated analogue of prostaglandin E1 available as 200  $\mu\text{g}$  and 100  $\mu\text{g}$  tablets. Misoprostol stimulates the myometrium causing uterine contractions and subsequently leading to abortion [3-5]. Fever, vomiting, and diarrhea are the major adverse effects of this drug [3-5]. With regard to its few adverse effects, low cost and ease of use, misoprostol is preferred over other prostaglandins for this purpose [7]. Vaginal route is safe and effective and the peak drug concentration is reached between 60 and 120 minutes after its application. Successful termination was generally considered as expulsion of the fetus within 48 hours with a success rate ranging from 60% to 100% [2-5, 7]. Previous studies have evaluated the efficacy of misoprostol at various doses, ranging from 100 mcg to 800 mcg, using a variety of routes and intervals of administration [5, 7]. The dose of misoprostol, however, has yet to be standardized. The authors used 400 mcg to 1,600 mcg misoprostol intravaginally with no significant side-effects. Although some researchers suggest that a shorter induction-to-abortion in-

Table 1. — The duration between onset of induction of abortion and expulsion with respect to demographic and clinical variables.

Variable	Average (range)	p value
Age	27.8 (16-47)	0.094
Gravida	4.4 (1-15)	0.513
Parity	2.8 (0-10)	0.607
Hemoglobin level (g/dl)	12.0 (6.1-18.0)	0.074
Platelet count ( $\text{mm}^3$ )	$263 \times 10^3$ (105-528 $\times 10^3$ )	0.735
Gestational age (weeks)	18.3 (15-26)	0.001*
Total misoprostol dose (mcg)	733 (400-1600)	< 0.001*
Blood glucose level (g/dl)	93.2 (51-187)	0.028*

\* Statistically significant.

terval might occur in patients receiving higher doses of misoprostol, others argue that poorer tolerance of those doses mitigates the benefit derived from hastening termination [3-5, 7]. Repetitive administrations of misoprostol are usually needed to induce abortion especially when used as a single agent [7-9].

In this retrospective study, it was shown that parameters with significant impact on the duration of abortion were gestational age at the time of induction, blood glucose level, and total dose of misoprostol applied. By interpretation of this data, accurate prediction of fetal expulsion within 24 h after the first induction attempt may be feasible.

The present findings are consistent with Dickinson's study, where 1,066 terminated pregnancies were achieved with 400 mcg vaginal misoprostol suppositories. Gestational age was found to have a significant effect impact on the time interval between the first induction and fetal expulsion [6]. Contrary to the present results, they had also suggested that maternal age and previous obstetric history also had an effect on the duration of abortion. The impact of prolonged induction time associated with increasing gestational age may be attributed to the need for greater cervical dilatation due to the increasing fetal size. Grigsby *et al.* demonstrated that with advancing gestational weeks, there is a reduction of some prostaglandin receptors in the maternal myometrium [10]. It could therefore be argued that prolonged induction interval with gestational age could be due to a reduction in the degree of responsiveness of the uterus to prostaglandins [8]. In contrast, Lo *et al.*, who examined 280 pregnancy terminations between 13 and 23 weeks by vaginal application of 400 mcg misoprostol, could not find a relationship between gestational age and the duration of TOP [11].

From the present results, the impact of gestational diabetes on the duration of abortion is noteworthy. The impact of blood glucose level on prolongation of the time interval may be associated with either macrosomia of fetus in diabetic mothers or decreased contractility of uterus in diabetes. The authors have not come across any publications in PubMed that mention the influence of diabetes on the duration of abortion. Therefore, this result renders the present study unique in this aspect and the authors suggest that further studies are necessary to investigate the effects of diabetes on abortion.

In contrast to these findings, the effect of the previous obstetric history on the duration of abortion procedure was observed by Jannet [12]. The time interval between the first induction and fetal expulsion was significantly shorter in multiparous than in primiparous women [13, 14]. This was explained by the more rapid ripening of the cervix after a previous spontaneous delivery [1, 13, 14]. Maternal side effects of oral prostaglandins, such as diarrhea, nausea, vomiting and were not significant in the present series where misoprostol was intravaginally administered.

The results also showed that gestational age was associated with the time interval from induction to complete abortion. This finding is in parallel with data from literature [1, 6]. However, the authors could not find a correlation between this time interval and parity. This is contradictory to some publications implying that nulliparous women required a significantly longer period of time to completely terminate fetal expulsion than multiparous women presumably due to alterations in cervical compliance [10,11].

The authors found that the total dose of misoprostol was increased in parallel to the prolongation of abortion process. However, this finding is not surprising since repeated doses of prostaglandins are administered in case the intended response is not achieved.

The main limitation of this study is its retrospective character. Further prospective research on this issue may yield more precise data on the parameters affecting the duration of abortion.

## Conclusion

Misoprostol is safe and effective for induction of abortion in second-trimester pregnancies. The time interval between induction and abortion is prolonged with advanced gestational age and higher blood glucose levels. Prospective randomized studies are necessary to better understand the factors influencing the duration of abortion.

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