Hourly Oral Misoprostol Administration for Terminating Midtrimester Pregnancies: A Pilot Study

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SUMMARY

Objective: This pilot study retrospectively evaluated the outcomes of medical induction of termination of midtrimester pregnancies with hourly oral misoprostol administration.

Materials and Methods: Sixteen women with living fetuses, who had undergone pregnancy termination at 12–25 weeks of gestational age, were reviewed. The method of induction was hourly oral administration of misoprostol, given at doses of 200 μg/hr for the first 12 hours and 400 μg/hr until 12 hours after delivery. Data including the induction-to-delivery interval and total dosage of misoprostol were recorded and analyzed.

Results: All 16 women successfully underwent vaginal termination within 36 hours. The median induction-to-delivery interval was 12.0 hours (range, 6.3–30.9 hours), with 13 women (81.3%) undergoing vaginal delivery within 24 hours. The median total dosage of misoprostol was 2,600 μg. The most common side effect was diarrhea, which was easily relieved by medication.

Conclusion: Our preliminary results show that oral administration of misoprostol at hourly intervals is a promising method for terminating midtrimester pregnancies. [*Taiwan J Obstet Gynecol* 2010;49(4):438–441]

Key Words: medical induction, midtrimester pregnancy, misoprostol

Introduction

A variety of management strategies have been reported for midtrimester pregnancy interruption [1,2]. Techniques include dilatation and evacuation, intra-amniotic prostaglandin $F_{2\alpha}$ instillation, prostaglandin E_2 (PGE_2) vaginal suppositories, intravenous high-dose oxytocin [3,4], a sulprostone infusion [5], and vaginal or oral administration of misoprostol [6–8]. Misoprostol, a potent uterotropic and uterotonic agent, which causes cervical effacement and dilation, and stimulates myometrial contractions, is effective in interrupting midtrimester pregnancies at gestational ages of 12–28 weeks. Several recent comparative investigations have demonstrated that the use of high-dose oral or vaginal misoprostol is more efficacious than alternative methods, such as concentrated oxytocin and PGE_2 administration, for interrupting midtrimester pregnancies, with an acceptable side-effect profile [9,10]. A high-dose, vaginal misoprostol regimen was superior to concentrated oxytocin plus low-dose PGE_2 in terms of the significantly shortened induction-to-delivery interval, fewer side effects, less medication for treatment of side effects, and a lower incidence of retained placenta requiring curettage [10]. Furthermore, compared with concentrated oxytocin plus low-dose vaginal misoprostol, high-dose vaginal misoprostol significantly shortened the time to induction of midtrimester labor in a later randomized trial [11].

Misoprostol may be administered via the oral, vaginal, or sublingual route. According to the pharmacokinetics of misoprostol [12,13], the sublingual and oral routes have the faster onset of action than vaginal

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administration, with or without water. Because the misoprostol tablet was developed for oral administration and not sublingual administration, most patients who take misoprostol sublingually experience an unpleasant taste. Therefore, oral administration is the easiest and has the greatest acceptability among women.

The ultimate goal of a successful strategy for interrupting midtrimester pregnancies is to combine efficacy (a shortened interval from induction to delivery) with minimal side effects and fewer cases of a retained placenta. Titrated oral misoprostol for induction of labor in the third trimester was more able to overcome the barrier of the cervix with no case of induction failure compared with vaginal misoprostol in our previous study [14]. Furthermore, because labor induction with a titrated oral misoprostol solution is effective and safe, it has been used as the standard method in our obstetric unit since 2004. Oral administration of misoprostol hourly was chosen because oral absorption is more rapid and possibly more predictable, with a peak serum concentration after oral administration of 34 minutes and a half-life of 20–40 minutes [13]. We reviewed patients who had undergone hourly oral misoprostol treatment for midtrimester pregnancy interruption at our labor and delivery unit to evaluate and analyze the outcomes.

Materials and Methods

We retrospectively reviewed the records of all women with living fetuses at 12–25 weeks of gestational age who electively underwent labor induction with hourly oral misoprostol administration to interrupt a midtrimester pregnancy at the Labor and Delivery Unit of China Medical University Beigang Hospital (Beigang, Taiwan) over a 4-year period from July 2004 to June 2008. Individual clinical case records were examined to confirm their authenticity and to collect details on management and outcomes. Women were excluded if clinical chorioamnionitis or spontaneous labor (regular uterine contractions with cervical change) were encountered. This study was approved by the institutional review board.

After patients without uterine surgery were admitted to our delivery unit and evaluated, we explained to them the method of hourly oral misoprostol administration to interrupt the pregnancy and its side effects including nausea, vomiting, diarrhea, and fever. The risk of uterine rupture was also discussed. Initially, one tablet of misoprostol 200 μg was given orally every hour. If the fetus had not been delivered within 12 hours, the oral dosage of misoprostol was increased to 400 μg/hr, from the 13th dose until expulsion of the fetus. Induction failure was defined as no fetal expulsion within 36 hours of initiation of induction. All side effects were recorded by obstetric nurses and were relieved using appropriate medication prescribed by the on-duty physician. If the placenta had not been delivered within 30 minutes after expulsion of the fetus, a retained placenta was recorded, and curettage was immediately performed.

The primary study outcomes for the investigation were the number of women who delivered their fetus vaginally within 12, 24 and 36 hours upon initiation of induction, the induction-to-delivery interval, and the total dosage of misoprostol administered. Secondary outcomes assessed included maternal side effects and complications. The entry characteristics of the patients including age, height, weight, parity, gestational age at induction, and fetal weight and birth length post-induction were also recorded. Descriptive statistics were use to analyze these data.

Results

Sixteen pregnant women (11 nullipara and 5 multipara) who met the entry criteria were reviewed in this study. Their demographic characteristics are given in Table 1. All 16 women electively underwent induction for psychosocial reasons. Eight women had completed vaginal delivery within 12 hours (50.0%; 3 nullipara and 5 multipara), and 13 had completed vaginal delivery within 24 hours (81.3%; 8 nullipara and 5 multipara). All 16 women had completed vaginal delivery within 36 hours (Table 2).

The median induction-to-delivery interval of all women was 12.0 hours (range, 6.3–30.9 hours). The median induction-to-delivery interval was 15.7 hours (range, 6.7–30.9 hours) for the nullipara group and 9.1 hours (range, 6.3–9.8 hours) for the multipara group. The median total dosage was 2,600 μg (range, 1,400–9,800 μg), while the median total dosage was 3,600 μg (range, 1,400–9,800 μg) for the nulliparous

Table 1. Maternal and fetal demographics (n = 16)*

Nullipara : Multipara	11 : 5
Age (yr)	18.2 (13.0–39.3)
Height (cm)	159 (146–170)
Weight (kg)	52 (40–74)
Gestation (wk)	17.0 (12.0–24.0)
Fetal weight (g)	100.0 (10.0–800.0)
Fetal birth length (cm)	19 (12–30)

**Data are presented as n or mean (range).*

Table 2. Outcomes of labor induction*

Outcome	Nullipara ($n=11$)	Multipara ($n=5$)	Total ($n=16$)
Vaginal delivery within 12 hr	3 (27.3)	5 (100)	8 (50.0)
Vaginal delivery within 24 hr	8 (72.7)	5 (100)	13 (81.3)
Vaginal delivery within 36 hr	11 (100)	5 (100)	16 (100)
Induction-to delivery interval (hr)	15.7 (6.7–30.9)	9.1 (6.3–9.8)	12.0 (6.3–30.9)
Total dosage of misoprostol (μg)	3600 (1,400–9,800)	1800 (1,400–2,000)	2600 (1,400–9,800)

**Data are presented as n (%) or median (range).*

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Table 3. Adverse obstetric outcomes ($n=16$)*

Retained placenta requiring curettage	1 (6.3)
Side effect	
Nausea	2 (12.5)
Vomiting	2 (12.5)
Diarrhea	8 (50.0)
Shivering	0 (0)
Pyrexia	2 (12.5)

**Data are presented as n (%).*

group and 1,800 μg (range, 1,400–2,000 μg) for the multiparous group.

Common side effects included diarrhea (50.0%), nausea and vomiting (12.5%), and pyrexia (12.5%). No shivering was seen. One woman (6.3%) required curettage due to a retained placenta.

Discussion

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Misoprostol is a strong agent which has uterotropin and uterotonin effects, and multiple trials have shown that misoprostol is an effective agent for cervical ripening and labor induction. Therefore, we developed a new hourly oral method of administering misoprostol, according to the mathematical model of the time to the peak serum concentration (T_{max}), half-life ($T_{1/2}$) after absorption, and uterine responsiveness.

Misoprostol does not affect the hepatic mixed-function oxidase enzyme systems. In patients with varying degrees of renal impairment, an approximate doubling of $T_{1/2}$, peak serum concentration (C_{max}), and area under the serum concentration curve were found when compared with normal patients, but no clear correlation between the degree of impairment and area under the serum concentration curve was shown. No routine dosage adjustment is recommended in older patients or patients with renal impairment. Misoprostol does not produce clinically significant effects on serum levels of prolactin, gonadotropin, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones, creatinine, or uric acid. Neither gastric emptying, immunologic competence, platelet aggregation, pulmonary function, nor the cardiovascular system is modified by the recommended doses of misoprostol. Therefore, the use of misoprostol is not contraindicated with renal disease, severe anemia, systemic lupus erythematosus, hypertension, or heart disease.

Parameters used to assess the efficacy of misoprostol were the interval from the first misoprostol dose to vaginal delivery, the percentage of women who delivered infants vaginally within 24 hours upon induction initiation, and the induction failure rate. It needs to be pointed out that our study did not include women with a dead fetus, because it is easier to successfully terminate a pregnancy via the vagina with a dead fetus than a living fetus. Our outcomes showed that the induction-to-delivery interval (12.0 hours) was shorter than that with a high-dose oral regimen (15.2 hours), which included dead fetuses [9]. Furthermore, in our study, 13 women (81.3%) including eight nulliparous and five multiparous women had completed vaginal termination within 24 hours. Induction failure did not occur among our cases. It is evident that the hourly oral regimen used for case management in our study was highly effective.

Parameters used to assess the safety were the total dosage and side effects of misoprostol. It needs to be understood that the safety of misoprostol has been documented at doses of up to 1,600 μg per day [15], but even higher dosages have been used with only mild side effects seen. To avoid misoprostol toxicity, induction failure was defined as no fetal expulsion within 36 hours of initiation of induction in our study. The maximum total dosage in our study group was 9,600 μg in a nulliparous woman, who experienced only the side effect of diarrhea. The most common side effect in our study was diarrhea (50.0%), which was tolerable due to the lack of recurrence after the pregnancy had been terminated. The side effects of pyrexia and shivering common in other studies with a high-dose oral or vaginal regimen were rare in our study. Only two women experienced pyrexia in our study group. One needed a total

dosage of 5,800 μg and the other needed 1,400 μg. In published case reports [16–18], accidental overdosing with misoprostol resulting in hyperthermia, hypoxia, and rhabdomyolysis all occurred with a single intake at a dosage exceeding 3,000 μg. Therefore, a probable reason for fewer side effects in our study was the steady serum level of misoprostol acid achieved with our regimen due to the 1 hour oral dosing interval with a small dosage. Thus the toxicity of misoprostol resulting from C_{max} can be avoided. However, one needs to remain alert to the possibility of misoprostol toxicity when the symptoms of pyrexia and shivering appear.

Uterine rupture and a retained placenta are two complications with the use of misoprostol. Even without a history of uterine surgery, a case of uterine rupture in a second trimester termination in combination with mifepristone was documented [19]. There was no case of uterine rupture in our study group. The usual reason for a retained placenta is failure of the retroplacental myometrium to contract, thus preventing detachment [20]. The retained placenta rate was 6.3% (1/16) in our study, which was lower than that with high-dose oral misoprostol in another study [9]. The method of hourly oral misoprostol suggests that steady contractions of the entire myometrium including the retroplacental site can be achieved by maintaining a steady serum concentration of misoprostol acid to avoid such a complication. Further study with more cases is required to prove this hypothesis.

Development of an optimal regimen for medical induction to terminate midtrimester pregnancies is ongoing. An ideal regimen is one that is effective, inexpensive, and easy to administer, and rapidly results in vaginal delivery. This pilot study suggests that hourly oral misoprostol administration is a promising method for terminating midtrimester pregnancies. Therefore, conducting a randomized controlled trial is required to compare hourly oral and high-dose vaginal misoprostol administration for interrupting midtrimester pregnancies.

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Author Queries

AQ1: Is this now correct? Also, is this the name of the board? If not, initial caps can be removed.
AQ2: Urotropin?
AQ4: Please provide citation for Table 3.