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FRONTIER

Individualized misoprostol dosing for labor induction or augmentation: A review

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Abstract

Cesarean birth rates are greater than 20% in many developed countries. The main diagnoses contributing to the high rate of cesarean births in nulliparous women are dystocia and prolonged labor. Traditionally, a policy of vaginal dinoprostone for the treatment of unripe cervix or early amniotomy with oxytocin administration for a ripened cervix has been associated with a modest reduction in the rate of cesarean births due to arrest disorders. However, the course of vaginal dinoprostone is tedious and oxytocin should be administered through an infusion pump, which may be inconvenient in certain settings. Because misoprostol has powerful uterotropic and uterotonic effects, and has become a common agent used in the practice of obstetrics and gynecology, the United States Food and Drug Administration removed the absolute contraindication of the drug during pregnancy from its label in April 2002. However, excessive uterine contractility resulting in tachysystole or fetal distress is always a concern with the oral or vaginal use of fixed-dosage misoprostol. Therefore, misoprostol should be administered with caution to ensure that fetal hypoxia does not occur. A pilot trial examining the use of very small, frequent, titrated oral misoprostol dosages administered every 2 h was first conducted by Hofmeyr *et al* in 2001. Given women's different metabolisms and responses to misoprostol, another method of titrating individualized oral misoprostol with dosing administered every hour relative to uterine response was then developed by Cheng in 2006. Based on previous studies, this titration method is potentially an ideal alternative to traditional dinoprostone, oxytocin or the previously established misoprostol dosing method for labor induction or augmentation.

Key words: Cervix; Misoprostol; Oxytocin; Labor induction; Labor augmentation

Core tip: Avoiding uterine tachysystole and fetal hypoxia is the critical consideration when implementing labor induction or augmentation with misoprostol. Titrated oral misoprostol is potentially an ideal alternative to traditional dinoprostone, oxytocin or the previously established misoprostol dosing method for labor induction or augmentation.

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BIOGRAPHY

Shi-Yann Cheng received his MD degree from National Yang-Ming University, Taipei, Taiwan. He completed an extensive 5-year obstetrics residency in Taiwan in the Department of Obstetrics and Gynecology, Veteran General Hospital, Kaohsiung. He is presently the Director of the Department of Obstetrics and Gynecology and Medical Education and Research at Medical China University Beigang Hospital and Lecturer in the School of Medicine

at Medical China University, Taichung, Taiwan. His research interests cover clinical obstetrics and interdisciplinary collaborative care education, and his most notable contribution is the development of the concept of labor induction with titrated misoprostol solution with a focus on dosing interval and uterine responses according to the pharmacokinetics of misoprostol. His CV lists 16 peer-reviewed publications, 2 book chapters, prestigious medical education devotion awards, and presentations at national and international meetings.

INTRODUCTION

There are many indications for term labor inductions and more than 15% of all gravid women require aid in cervical ripening. A labor course longer than that of spontaneous labor is the most commonly encountered problem associated with labor induction. Additionally, prolonged spontaneous labor in nulliparous women is another common problem that can result in a negative birth experience[1,2] and can be associated with a non-reassuring fetal heart rate (FHR) resulting in emergency cesarean delivery[3,4]. Considering the root cause of these problems, the unripe cervix is the greatest barrier to spontaneous birth, which results in great concern and unnecessary cesarean deliveries. Therefore, overcoming an unripe cervix is a critical issue. Misoprostol, a synthetic prostaglandin E1 analogue, was initially used to treat peptic ulcers caused by prostaglandin synthetase inhibitors. Because misoprostol has been used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage, the absolute contraindication of the use of misoprostol during pregnancy was removed from the label by the United States Food and Drug Administration in April 2002[5]. Because misoprostol has powerful uterotropic and uterotonic effects, many studies have been conducted since 1992 to learn how to administer the drug while taking into consideration safety during labor induction[6-9]. Fetal hypoxia resulting from uterine tachysystole is always an obstetrical concern[10-16]. The recommended dosage of misoprostol is 50 μg every 4 h *via* the oral route or 25 μg every 4 h *via* the vaginal route[17] until adequate labor commences, but the induction duration is prolonged. Because the risk of inducing fetal hypoxia is incurred by using a fixed dosage of misoprostol, a pilot trial using very small, frequent, titrated oral misoprostol doses every 2 h was first conducted by Hofmeyr *et al*[18,19] in 2001. It was concluded that this new approach to oral misoprostol administration was successful in minimizing the risk of uterine hyperstimulation, which has been a feature of misoprostol use for labor induction, at the expense of a somewhat slower response in women with intact membranes and unfavorable cervices[19]. Given women's different metabolic rates and responses, another method of titrating individualized oral misoprostol with dosing administered every hour relative to uterine response was developed[20-23]. It was observed that a higher success rate of vaginal delivery within 24 h, not accompanied by a higher rate of uterine hyperstimulation, was achieved using the 1-h oral misoprostol titration method (Table 1). According to the results of titration studies, misoprostol is the ideal candidate agent for labor induction and augmentation due to its convenience of administration and cervical ripening characteristics.

PRINCIPLE OF TITRATED ORAL MISOPROSTOL ADMINISTRATION

After misoprostol is absorbed, it undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and is detectable in the blood plasma[26]. Because misoprostol's effects on and toxicity to the uterus based on serum concentrations of misoprostol acid at term are unknown, the rationale for titrated administration stems from the proven efficacy and pharmacokinetics of misoprostol, and the extreme inter- and intra-individual variation in uterine sensitivity[20]. To avoid uterine hyperstimulation and shorten the labor course, misoprostol should be administered in small, frequent doses (one dose per hour, generally) titrated against the uterine response. This approach is analogous to the conventional, titrated use of oxytocin. Currently, misoprostol is available as an oral tablet of 100 or 200 μg and is water-soluble. Oral administration is easier and has greater acceptability among women than vaginal administration. Because the drug absorption is more rapid and more predictable, with a peak serum concentration after oral administration of 34 min and a half-life of 20-40 min[26], a 1-h interval between oral administrations and an increase in dosage of 20 μg every 4 h from the initial 20-μg dosage were determined to be optimal, based on a mathematical model that takes these drug characteristics into consideration[20]. This method maintains a virtually steady serum level of misoprostol acid, thus avoiding large fluctuations and increases the peak serum concentration of the 20-μg absorptive misoprostol dose every 4 h by a factor of 1.33. This mathematical model is described in Table 2.

CLINICAL PHARMACOLOGY OF MISOPROSTOL

Misoprostol does not affect the hepatic mixed-function oxidase enzyme systems. In patients with varying degrees of renal impairment, there is an approximate doubling of the $T_{1/2}$, peak serum concentration (C_{max}), and area under the serum concentration curve compared with those of normal patients, but no clear correlation between the degree of impairment and area under the serum concentration curve has been shown. No routine dosage adjustment is recommended in older patients or patients with renal impairment[27,28]. Misoprostol does not produce clinically significant effects on the serum levels of prolac-

Table 1 Comparison of titrated oral misoprostol in labor induction between studies

Ref.	Year	No. of women	Initial dosage (μg)	Dosing interval	Efficacy	Adverse effects	Cesarean rate (%)
Hofmeyr *et al*[18]	2001	25	20	q2h	72% VD within 32 h	8% UH	20.0
Hofmeyr *et al*[19]	2001	346	20	q2h	62% VD within 24 h	4% UH	16.0
Matonhodze *et al*[24]	2003	176	20	q2h	60.2% VD within 24 h	4% UH, 8% UT	14.0
Cheng *et al*[20]	2006	77	20	q1h	93.5% VD within 24 h	0% UH, 9.1% UT	3.9
Bricker *et al*[25]	2008	375	20	q2h	76% VD within 24 h	2% UH, 5% UT	14.0
Cheng *et al*[21]	2008	101	20	q1h	94.1% VD within 24 h	0% UH, 6.9% UT	4.0
Ho *et al*[22]	2010	112	20	q1h	94.6% VD within 24 h	0% UH, 7.1% UT	3.6
Souza *et al*[23]	2010	30	20	q1h	80% VD within 24 h	13.3% UT	20.0

VD: Vaginal delivery; UH: Uterine hyperstimulation; UT: Uterine tachysystole.

Table 2 Mathematical model of titrated oral misoprostol

	Times $t = 34 + 60n$, $n = 0, 1, 2, 3, \text{---}$ (min)				
Dosage (mcg)	34	94	154	214	274
20	P				
20		$P(1/4^0 + 1/4^1)$			
20			$P(1/4^0 + 1/4^1 + 1/4^2)$		
20				$P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3)$	
40					$P + P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3 + 1/4^4)$
…					

Set the function C = f(t), where C: Concentration of misoprostol acid (pg/mL) in plasma; t: Times during the whole process, $t = 34 + 60n$ (min), when taking misoprostol at $n = 0, 1, 2, 3, \text{---}$ (h); T_{max} (the time to peak plasma concentration of misoprostol acid after absorption): 34 min; $T_{1/2}$ (the half-life of misoprostol acid): 30 min as determined by a pharmacokinetics study. When $n = 0$, intake 20 μg, $t = 34$ min, set the peak plasma concentration of misoprostol acid, C = P; When $n = 1$, intake 20 μg, $t = 34 + (60 \times 1) = 94$ min, and $C = P(1/4^0 + 1/4^1)$; When $n = 2$, intake 20 μg, $t = 34 + (60 \times 2) = 154$ min, and $C = P(1/4^0 + 1/4^1 + 1/4^2)$; When $n = 3$, intake 20 μg, $t = 34 + (60 \times 3) = 214$ min, and $C = P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3)$; When $n = 4$, intake 40 μg, $t = 34 + (60 \times 3) = 214$ min, and $C = P + P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3 + 1/4^4)$ and so on. Therefore, C = f(t) is a convergent series in which the upper limit = P/(1 - 1/4) + P/(1 - 1/4) + --- = (4/3)P + (4/3)P + ---.

tin, gonadotropin, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones, creatinine or uric acid. Furthermore, gastric emptying, immunological competence, platelet aggregation, pulmonary function and the cardiovascular system are not modified by the recommended doses of misoprostol[28]. Therefore, the use of misoprostol is not contraindicated in patients with renal disease, severe anemia, systemic lupus erythematosus, hypertension or heart disease.

RISKS OF MISOPROSTOL ADMINISTRATION

Uterine rupture is an unwanted risk of labor regardless of whether a woman has had a previous caesarean delivery. Most studies suggest that the use of misoprostol in women with a previous caesarean delivery increases the frequency of uterine scar disruption, either described as uterine dehiscence or overt uterine rupture[29-31]. There are even sporadic reports of uterine rupture in women without prior cesarean surgeries[32,33]. Grand multiparity appears to be a risk factor for uterine rupture in the presence of misoprostol, although there is a report of uterine rupture in a primigravida[34]. Therefore, the indications for labor induction or augmentation must be carefully evaluated prior to misoprostol administration.

PREPARING ORAL MISOPROSTOL SOLUTIONS AND GUIDELINES FOR ADMINISTRATION

Misoprostol is manufactured as an oral tablet and is water-soluble. The uterine activity produced by an oral solution is faster and stronger than that produced by an oral tablet or when administered *via* the rectal or vaginal route[35]. One 200-μg tablet of misoprostol may be dissolved in 200 mL of drinking water in a medicine bottle. The misoprostol solution needs to be used completely within 24 h after preparation or discarded. Women are induced with one basal unit of 20 mL of misoprostol solution (1 μg/mL) prepared as described above. The determined volume of misoprostol solution is poured according to the obstetrician's discretion at each dosing, following the guidelines of labor induction[21] or augmentation[22]. Initially, the determined volume may be given upon request by an obstetrician according to the guidelines when regular uterine contractions are not achieved. Once regular uterine contractions are achieved, the obstetrician is called to visit the patient and make a decision regarding the next dose or dosage adjustment, if any. Such individualized administration of misoprostol decreases the accidental fetal hypoxia resulting from uterine hyperstimulation. The flowchart of administration is shown in Figure 1. The

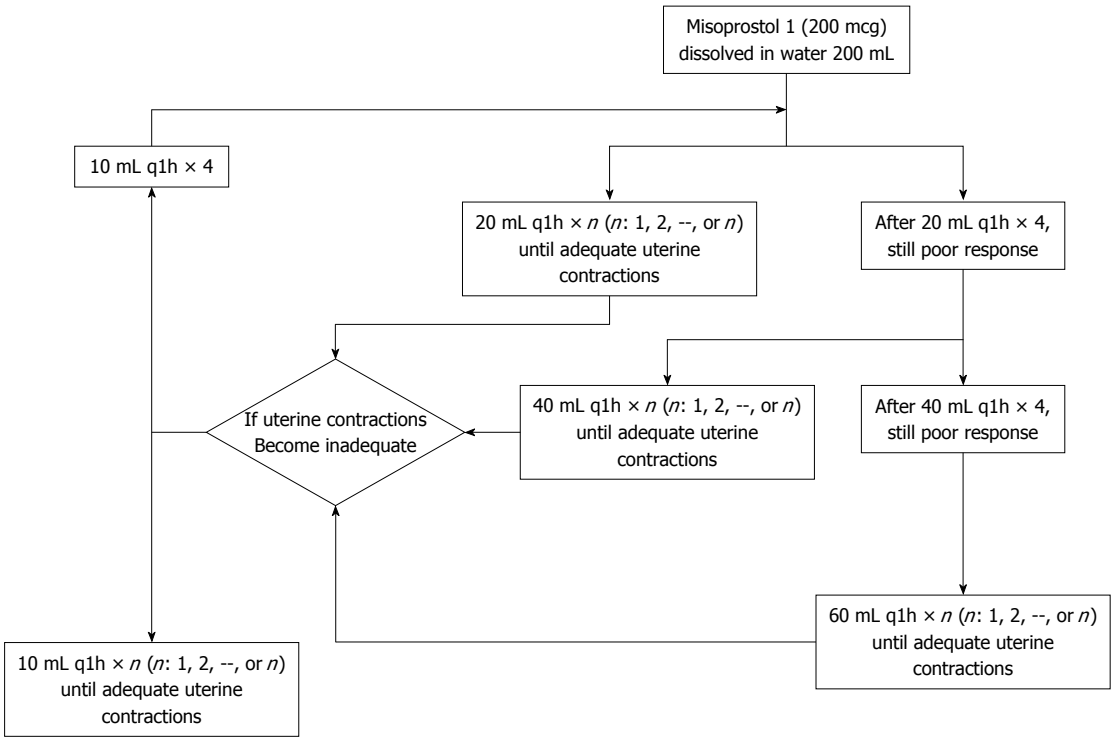

Figure 1 Flowchart of misoprostol administration.

general misoprostol administration guidelines are as follows: (1) An initial dose of 20 μg/h is administered and repeated hourly until adequate uterine contractions are achieved. If contractions do not occur after 4 doses, the dosage is increased to 40 μg/h and repeated hourly until uterine contractions are achieved, for a maximum of 4 more doses. If the response still remains poor after 8 h, the dosage can be increased to 60 μg/h until adequate contractions occur or a maximum cumulative dosage of 1600 μg is reached; (2) Adequate uterine contractions are defined as 3 or more contractions in a 10-min period, over 30-min windows. Once uterine activity is adequate for a 1-h period, no further misoprostol is administered; (3) If the contractions subsequently become inadequate, hourly doses of misoprostol solution are started at 10 μg/h and can be increased to 20 μg/h, and perhaps 40 μg/h, based on uterine responsiveness. This process is repeated until adequate uterine contractions occur or a maximum cumulative dosage of 1600 μg is reached; (4) FHR and uterine activity are continuously monitored throughout the active phase of the labor course; (5) Induction failure is defined as not entering the active phase of labor after 36 h of misoprostol treatment, with a maximum cumulative dosage of 1600 μg. Failure to progress is defined as cervical dilation or fetal descent without any progress for 3 h after entering the active labor phase; (6) Intravenous magnesium sulfate (4 g over 30 min) or any other tocolytic agent available should be given at the physician's discretion if uterine hyperstimulation occurs; (7) When the cervix achieves a Bishop score of 9, the artificial rupture of the membrane can be performed at the physician's discretion; (8) The active phase is defined as the achievement of adequate uterine contractions with a cervical dilatation of greater than 3 cm; (9) Supplemental oxytocin can be used at the physician's discretion when uterine contractions are inadequate or when entering into the active phase of labor with a favorable cervix (Bishop score > 8) because of poor response to misoprostol; and (10) Cesarean delivery is offered to all patients after induction failure, after failure of labor to progress, or when non-reassuring FHR patterns occur.

INDICATIONS AND CONTRAINDICATIONS FOR MISOPROSTOL ADMINISTRATION

The indications for labor induction with titrated oral misoprostol are the same as those for labor induction with oxytocin, including post-term pregnancy, preeclampsia, diabetes mellitus, oligohydramnios, intrauterine fetal growth restriction, and abnormal antepartum fetal surveillance results. However, to avoid adverse events, it is important for practitioners to be alert to contraindications, including a non-reassuring FHR pattern, uterine scarring, grand multiparity (≥ 5), any contraindication for labor or vaginal delivery or both, suspected placental abruption with an abnormal FHR pattern, and hypersensitivity to misoprostol or prostaglandin analogues.

ADVERSE EFFECTS AND TERATOGENICITY OF MISOPROSTOL

In published case reports[36-38], accidental overdosing with misoprostol resulted in pyrexia, hypoxia and rhabdomy-

olysis; all occurred with a single drug intake at a dosage exceeding 3000 μg. These adverse effects are signs of misoprostol toxicity and can be easily monitored when administering misoprostol. The other common side effects are nausea, vomiting and diarrhea, but these side effects rarely occur in the course of labor induction or augmentation with titrated oral misoprostol. Furthermore, these side effects are easily relieved by medication.

First trimester exposure to misoprostol is associated with facial paralysis[39], limb defects or vascular disruption defects[40,41] in newborns. In the Latina American Collaborative Study of Congenital Malformations of 4673 malformed infants and 4980 control infants, increased frequencies of transverse limb defects, ring-shaped constrictions of the extremities, arthrogryposis, hydrocephalus, holoprosencephaly and bladder exstrophy, but not Mobius syndrome, were observed in the infants exposed to misoprostol in utero[42]. There are no known reports of teratogenicity upon misoprostol ingestion when taken after the first trimester.

EFFICACY OF TITRATED ORAL MISOPROSTOL

The 1-h interval between titrated oral misoprostol administration based on pharmacokinetics has been proven to be effective in previous studies. One randomized controlled trial of titrated misoprostol compared titrated oral with vaginal misoprostol for labor induction[21]. Women between 34 and 42 wk of gestation with an unfavorable cervix (Bishop score ≤ 6) and an indication for labor induction were randomly assigned to receive titrated oral or vaginal misoprostol. The titrated oral misoprostol group received a basal unit dose of 20 mL of misoprostol solution (1 μg/mL) every hour for 4 doses, then with titration based on individual uterine responses. The vaginal group received 25 μg every 4 h until attaining a more favorable cervix. Vaginal delivery within 12 h was the primary outcome. The data were analyzed on an intention-to-treat basis. Titrated oral misoprostol and vaginal misoprostol were given to 101 (48.8%) and to 106 (51.2%) women, respectively. Completed vaginal delivery occurred within 12 h in 75 (74.3%) women in the titrated oral group and 27 (25.5%) women in the vaginal group ($P < 0.01$; RR = 8.44; 95%CI: 4.52-15.76). Four women (4.0%) in the titrated oral group and 18 (17.0%) women in the vaginal group underwent cesarean deliveries ($P < 0.01$; RR = 0.20; 95%CI: 0.07-0.62). The incidence of hyperstimulation was 0.0% in the titrated oral group compared with 11.3% in the vaginal group ($P < 0.01$; RR = 0.08; 95%CI: 0.01-0.61). Although more women experienced nausea (10.9%) in the titrated oral group ($P < 0.01$; RR = 27.07; 95%CI: 1.57-465.70), fewer infants had Apgar scores of less than 7 at 1 min in the titrated oral group compared with the vaginal group ($P < 0.01$; RR = 0.10; 95%CI: 0.01-0.76). The conclusion was that titrated oral misoprostol was associated with a lower incidence of uterine hyperstimulation and a lower cesarean delivery rate than vaginal misoprostol for labor induction in patients with unfavorable cervix.

Another randomized controlled trial compared oral titrated misoprostol with intravenous oxytocin for labor augmentation in women at 36-42 wk of gestation with spontaneous onset of active labor[22]. Women meeting the general selection criteria of having regular contractions, an effaced cervix dilated between 3 and 9 cm, and inadequate uterine contractions (2 or fewer contractions every 10 min) during the first stage of labor, were randomly assigned to titrated oral misoprostol or intravenous oxytocin. The augmentation-to-vaginal delivery interval and occurrence of vaginal delivery within 12 or 24 h were the primary outcomes. The data were analyzed on an intention-to-treat basis. Of the 231 women, 118 (51.1%) and 113 (48.9%) were randomized to titrated oral misoprostol and titrated intravenous oxytocin, respectively. The median interval from the start of augmentation to vaginal delivery was 5.22 h (3.77-8.58 h, 25th-75th percentile) in the misoprostol group, and 5.20 h (3.23-6.50 h, 25th-75th percentile) in the intravenous oxytocin group ($P = 0.019$). Complete vaginal delivery occurred within 12 h for 92 (78.0%) women in the misoprostol group and 97 (85.8%) women in the oxytocin group ($P = 0.121$; RR = 0.91; 95%CI: 0.80-1.03). There were no significant differences between the 2 groups who delivered vaginally within 24 h. Twelve (10.2%) women in the misoprostol group and 13 (11.5%) women in the oxytocin group underwent cesarean deliveries ($P = 0.744$; RR = 0.88; 95%CI: 0.42-1.85). The side effects and neonatal outcomes also did not differ between the two groups. The conclusion was that labor augmentation with titrated oral misoprostol or intravenous oxytocin resulted in similar rates of vaginal delivery within 12 and 24 h.

A retrospective review of the medical records of all patients between 37 and 42 wk of gestation with a Bishop score ≤ 6 who underwent labor induction with titrated oral misoprostol solution[43] has also been conducted. The women were allocated into two groups: nulliparous and multiparous. The women received one basal unit of misoprostol solution (20 mL, 1 μg/mL) every hour for four doses; additional doses were titrated based on individual uterine responses. The latent and active phase intervals and occurrence of vaginal delivery within 12 h were the primary outcomes. Of the 112 women included in the study, 49 (43.8%) nulliparae and 63 (56.2%) multiparae underwent labor induction with titrated oral misoprostol solution. Although fewer women delivered vaginally within 12 h in the nulliparous group than in the multiparous group (42.9% *vs* 85.7%; $P < 0.01$; RR = 0.54; 95%CI: 0.39-0.76), there was no significant difference between the two groups regarding vaginal delivery within 24 h (87.8% *vs* 100.0%; $P = 0.09$; RR = 0.96; 95%CI: 0.90-1.02). Four (8.2%) women in the nulliparous group and none (0.0%) of the women in the multiparous group underwent caesarean deliveries ($P = 0.02$; RR = 1.09; 95%CI: 1.00-1.18). All induction durations, including the latent and active phases, were significantly shorter in the multiparous

group ($P < 0.01$). Induction failure did not occur in any patient in either of the groups. There was no instance of hyperstimulation, which was defined as tachysystole or hypertonus with a non-reassuring FHR pattern, although tachysystole, defined as the presence of at least 6 contractions in 10 min over at least 2 10-min windows, occurred in 4 (8.2%) nulliparous women and 4 (6.3%) multiparous women. Hypertonus, defined as a single contraction lasting more than 2 min, did not occur in either group. None of the neonates in either group had Apgar scores of < 7 at 1 min. The conclusion was that titrated oral misoprostol solution was a promising method of labor induction for both nulliparous and multiparous women.

SUMMARY AND FUTURE PROSPECTS

Cesarean birth rates are greater than 20% in many developed countries[44]. The main diagnoses contributing to the high rate of cesarean births in nulliparous women are dystocia and prolonged labor. Traditionally, a policy of vaginal dinoprostone for the treatment of an immature cervix or early amniotomy with oxytocin administration for mature cervices for the prevention of a delay in labor progress is associated with a modest reduction in the rate of cesarean births[45]. However, the course of vaginal dinoprostone or misoprostol is tedious, and excessive uterine contractility resulting in fetal distress is always a concern with the oral or vaginal use of fixed-dosage misoprostol. Oxytocin administration through the intravenous route needs to be under the control of an intravenous pump and may be inconvenient in certain settings. Because titrated oral misoprostol solution is easier to administer than titrated intravenous oxytocin, it is worth conducting these treatment regimens for labor induction or augmentation. In addition, misoprostol offers several advantages over dinoprostone and oxytocin, including a longer shelf life, stability at room temperature, and easy administration. It is an ideal alternative to traditional dinoprostone or oxytocin for labor induction or augmentation. In consideration of inter- and intra-individual variations of drug response during the dosing course, it is reasonable that the titrated oral misoprostol solution may replace fixed-dosage misoprostol *via* the vaginal or oral route for labor induction or augmentation. In addition, the use of titrated oral misoprostol is superior to the traditional use of vaginal misoprostol in completing vaginal deliveries to reduce the cesarean rate, based on previous randomized controlled trials[21]. However, further studies are needed to determine the minimal plasma misoprostol concentration necessary to induce a uterine response during labor induction at term and to validate the mathematical model of titrated oral misoprostol. This information will help ensure the obstetric use of misoprostol.

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