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How to Manage Labor Induction or Augmentation to Decrease the Cesarean Deliveries Rate

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1. Introduction

There are many indications for term labor inductions and more than 15% of all gravid women require aid in cervical ripening and labor induction. That their labor courses are longer than that of spontaneous labor is the most common met problem. The prolonged course of spontaneous labor among nulliparous women is another common problem. They can result in a negative birth experience (Waldenstrom et al. 2004; Nystedt et al. 2006) and can be associated with non-reassuring fetal hear rate (FHR) resulting in emergency cesarean delivery (Bugg et al. 2006; Florica et al. 2006). When we think over the root cause of these problems, the immature cervix is the greatest barrier, which results in more concerned and unnecessary cesarean deliveries. Therefore, how to break through the immature cervix is the critical point. Misoprostol, a synthetic prostaglandin E1 analogue, was initially used to treat peptic ulcers caused by prostaglandin synthetase inhibitors, and was approved by the U.S. Food and Drug Administration for obstetric use in April 2002 (ACOG Committee Opinion. Number 283, May 2003. New U.S. Food and Drug Administration labeling on Cytotec (misoprostol) use and pregnancy 2003). Because the misoprostol has powerful uterotropic and uterotonic effect, there have been many researches to conduct clinical trials to learn how to administrate this agent under consideration of safety for labor induction since 1992 (Keirse 1993; Sanchez-Ramos et al. 1993; Hofmeyr et al. 1999; Wing 1999). The fetal hypoxia resulted from uterine hyperstimulation under administration of misoprostol is always a concern (Bennett et al. 1998; Kolderup et al. 1999; Hofmeyr &Gulmezoglu 2001; Shetty et al. 2001, 2002a; Shetty et al. 2002b; Alfirevic &Weeks 2006). The recommended dosage of misoprostol so far is 50 mcg per 4 hours via oral route (Alfirevic &Weeks 2006) or 25 mcg per 4 hours via vaginal route (Weeks &Alfirevic 2006), but the induction interval is too long. In consideration of individuals with different metabolism and response, the fixed-dosage of misoprostol will give risk of fetal hypoxia. Therefore, the individualized administrating method of titrated oral misoprostol against uterine response was developed (Cheng et al. 2008; Ho et al. 2010).

2. Principle of titrated oral misoprostol administration according to uterine response and pharmacokinetics

After misoprostol is absorbed, it undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and is detectable in plasma (Zieman et al. 1997). Because

the minimal effect and toxicity of serum concentration of misoprostol acid for uterus at term are unknown, the rationale for titrated administration stems from the proven efficacy and pharmacokinetics of misoprostol, and the extreme interindividual and intraindividual variation in terms of uterine sensitivity (Cheng et al. 2008). To avoid uterine hyperstimulation and shorten the interval of labor course, the principle is that misoprostol should be administered in small, frequent doses (one dose per hour generally), titrated against uterine response and analogous to the conventional titrated use of oxytocin. The misoprostol is manufactured as an oral tablet 100 or 200 mcg so far and is water-soluble. The oral administration is easier and has greater acceptability among women. Because the 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 (Zieman et al. 1997), the 1-hour interval between oral administrations and the increasing dosage of 20 mcg every 4 hours from initial 20 mcg are determined based on this mathematical model of the time to peak serum concentration and half-life of oral misoprostol after absorption. This method virtually maintains a steady serum level of misoprostol acid without large fluctuations and increases by one and one third the peak serum concentration of 20 mcg absorptive misoprostol every four hours. This mathematic model is described as figure 1.

	times t=34+60n n=0,1,2,3, --- (minutes)					
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 (minutes), when intake misoprostol at n=0, 1, 2, 3, ---(hours)

T_{max} (the time to peak plasma concentration of misoprostol acid after absorption): 34 minutes

$T_{1/2}$ (the half-life of misoprostol acid): 30 minutes were already determined according to pharmacokinetics study

When at n=0, intake 20 mcg, t=34 minutes, set the peak plasma concentration of misoprostol acid, C=P

When at n=1, intake 20 mcg, t=34＋(60×1)=94 minutes, then $C=P(1/4^0+1/4^1)$

When at n=2, intake 20 mcg, t=34＋(60×2)=154 minutes, then $C=P(1/4^0+1/4^1+1/4^2)$

When at n=3, intake 20 mcg, t=34＋(60×3)=214 minutes, then $C=P(1/4^0+1/4^1+1/4^2+1/4^3)$

When at n=4, intake 40 mcg, t=34＋(60×3)=214 minutes, then $C=P+P(1/4^0+1/4^1+1/4^2+1/4^3+1/4^4)$

…

Therefore, the C=f(t) is convergent series, the upper limit=P/(1-1/4)＋P/(1-1/4)＋---

=(4/3)P＋(4/3)P＋---

Fig. 1. Mathematic Model of Titrated Oral Misoprostol

3. Clinical pharmacology of misoprostol

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.

4. Risk of misoprostol administration

The uterine rupture is the unwanted risk no matter what it happen to women with or without previous caesarean surgery. Most study suggest that the use of misoprostol in women with previous caesarean delivery increases the frequency of uterine scar disruption, either described as uterine dehiscence or over uterine rupture (Wing et al. 1998; Blanchette et al. 1999; Choy-Hee &Raynor 2001). There are sporadic reports of spontaneous uterine rupture in women without prior surgery (Bennett 1997; Khabbaz et al. 2001). Grand multiparity seems to be a risk factor, although a report of uterine rupture in a primigravida also exists (Thomas et al. 2003). Therefore, the conditions to give labor induction or augmentation need to be evaluated in advance.

5. Indication and contraindications to administer misoprostol

5.1 Indications and contraindications of labor induction with titrated oral misoprostol

The indications of labor induction with titrated oral misoprostol include postterm pregnancy, preeclampsia, diabetes mellitus, oligohydramnios, intrauterine fetal growth restriction, and abnormal antepartum fetal surveillance results. The contraindications include nonreassuring FHR pattern, uterine scar, grand multiparity($\geqq$5), any contraindication to labor or vaginal delivery or both, suspected placental abruption with abnormal FHR pattern and hypersensitivity to misoprostol or prostaglandin analogues.

5.2 Indicaitons and contraindications of labor augmentation with titrated oral misoprostol

Women with reassuring FHR pattern and developing inadequate uterine contractions (two or fewer contractions per 10 minutes) for at least 30-minute windows during the labor course are indicated for labor augmentation with titrated oral misoprostol. The contraindications include nonreassuring FHR pattern, uterine scar, grand multiparity($\geqq$5), any contraindication to labor or vaginal delivery or both, suspected placental abruption with abnormal FHR pattern and hypersensitivity to misoprostol or prostaglandin analogues.

6. Procedure of preparing oral misoprostol solution and guidelines of 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 of an oral tablet, or when given via the rectal or vaginal route (Chong et al. 2004). One tablet of misoprostol is 200 mcg and may be dissolved in 200 ml of tap water in a medicine bottle. The misoprostol solution needs to be used completely within 24 hours after preparation or discarded. Women are induced with one basal unit of 20 ml of misoprostol solution (1 mcg/ml) prepared as described above. The determined volume of misoprostol solution will be poured according to obstetrician's discretion at each dosing following the guidelines of labor induction (Cheng et al. 2008) or augmentation (Ho et al. 2010). Initially, the determined volume may be given at obstetrician's order according to the guidelines when the regular uterine contractions are not achieved. Once the regular uterine contractions are achieved, the obstetrician will be called to visit and make decision of next step. Therefore, the individualized administration of misoprostol will avoid the accident issue of fetal hypoxia resulted from uterine hyperstimulation. The flowchart of administration is showed as Figure 2 and the guidelines are also described as the followings.

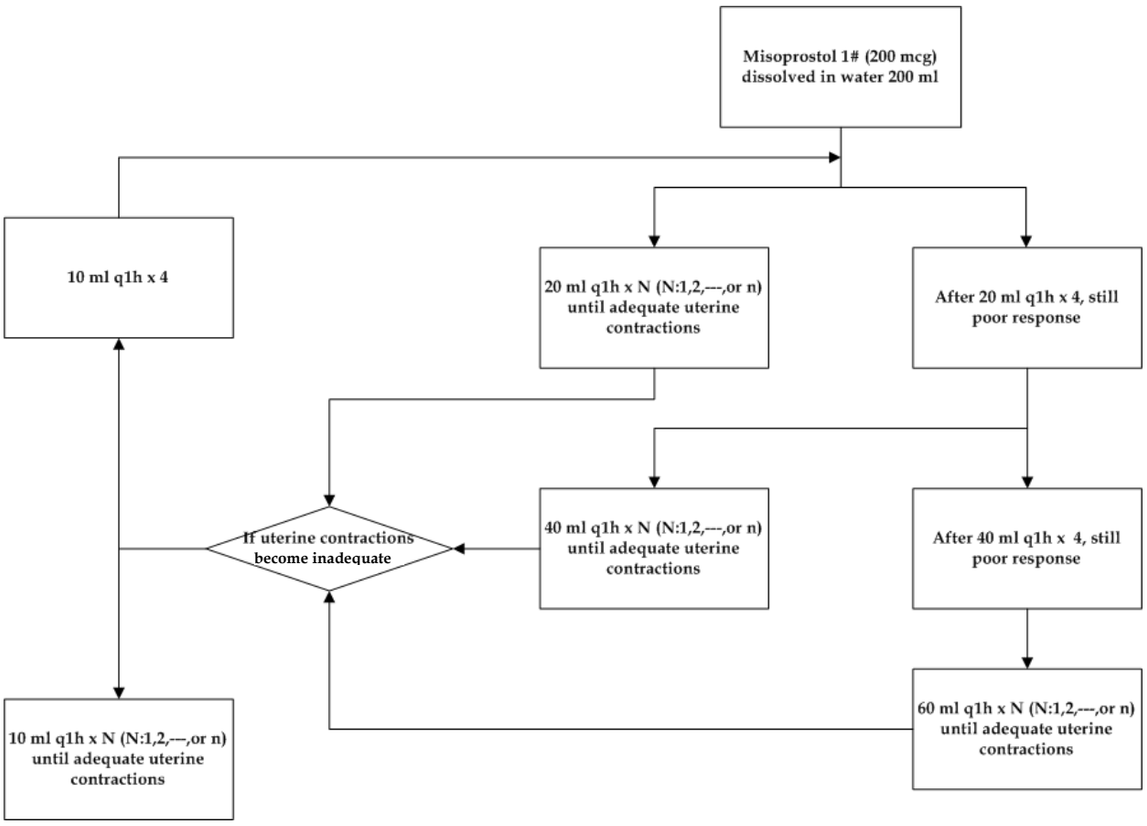

Fig. 2. Flowchart of administration

6.1 The guidelines of titrated oral misoprostol administration in labor induction

1. The initial dose of 20 mcg/h is administered until adequate uterine contractions are achieved. If contractions do not occur after four doses, the dosage is increased to 40 mcg/h and repeated every hour until uterine contractions are achieved, for a maximum of four more doses. If response still remains poor after 8 h, the dosage could be increased to 60 mcg/h until adequate contractions occur. The usual 'nil by mouth' rule is not enforced during the latent phase of the labor course.
2. Adequate uterine contractions are defined as three or more in 10 minutes over 30-minute windows. Once uterine activity is adequate over 1 hour, no further misoprostol is given.
3. If contractions subsequently become inadequate, hourly doses of misoprostol solution are started at 10 mcg/h and could be increased to 20 mcg/h and perhaps 40 mcg/h based on uterine responsiveness. This process is repeated until adequate uterine contractions occur.
4. Fetal heart rate and uterine activity are continuously monitored throughout labor induction.
5. Induction failure is defined as not entering the active phase after 36 h of misoprostol treatment, with a maximum cumulative dosage of 1600 mcg. Failure to progress is defined as the cervical dilation or fetal descent without any progress for 3 hours after entering the active labor phase as augmented by the agent.
6. Intravenous magnesium sulfate (4 g over 30 min) could be given at the physician's discretion if uterine hyperstimulation occur.
7. When the cervix achieved a Bishop score of 9, artificial rupture of the membrane could be performed at the physician's discretion.
8. The active phase is defined as achieving adequate uterine contractions with cervical dilatation greater than 3 cm.
9. Supplemental oxytocin could be used at the physician's discretion when uterine contractions are inadequate or when entering into the active phase with a favorable cervix (Bishop score > 8) because of poor response to misoprostol.
10. Failure to progress is defined as the cervical dilation or fetal descent without any progress for 3 hours after entering the active labor phase as augmented by the agent.
11. Cesarean section will be offered to all patients after induction failure, failure of labor to progress or when nonreassuring FHR occur.

6.2 The guidelines of titrated oral misoprostol administration in labor augmentation

1. Misoprostol is initially administered at a dose of 20 mcg/h until adequate uterine contractions are achieved. If contractions do not occur after 4 hours (four doses), the dosage could be increased to 40 mcg and repeated every hour until uterine contractions occurred. Nothing by mouth, except medication, was allowed during the active phase of labor.
2. Adequate uterine contractions are defined as three or more in 10 minutes over 30-minute windows. Once uterine activity is adequate over 1 hour, no further misoprostol is given.
3. If contractions subsequently become inadequate, hourly doses of misoprostol solution are started at 10 mcg/h and could be increased to 20 mcg/h and to as much as 40 mcg/h based on uterine responsiveness. This process is repeated until adequate uterine contractions occur.

4. Both fetal heart rate and uterine activity are continuously monitored throughout labor augmentation.
5. The maximum cumulative dosage of misoprostol is 1,600 mcg.
6. Intravenous magnesium sulfate (4 g over 30 minutes) could be given at the discretion of the physician if uterine hyperstimulation occur.
7. When the cervix achieved a Bishop score of 9, artificial rupture of the membrane could be performed at the physician's discretion.
8. The active phase is defined as achieving adequate uterine contractions with cervical dilatation greater than 3 cm.
9. Failure to progress is defined as the cervical dilation or fetal descent without any progress for 3 hours after entering the active labor phase as augmented by the agent.
10. Cesarean delivery is offered to all patients after failure of labor to progress or when nonreassuring FHR occur.

7. Efficacy of titrated oral misoprostol

The hourly misoprostol administration which is based on pharmacokinetics proves to be effective from the following studies.

7.1 The efficacy of titrated oral misoprostol for labor induction

There is one randomized controlled trial was to compare titrated oral with vaginal misoprostol for labor induction (Cheng et al. 2008). Women between 34 and 42 weeks of gestation with an unfavorable cervix (Bishop score less than or equal to 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 of 20 mL misoprostol solution (1 mcg/mL) every 1 hour for four doses and then were titrated against individual uterine response. The vaginal group received 25 mcg every 4 hours until attaining a more favourable cervix. Vaginal delivery within 12 hours was the primary outcome. The data were analyzed by intention-to-treat. Titrated oral misoprostol was given to 101 (48.8%) women and vaginal misoprostol to 106 (51.2%) women. Completed vaginal delivery occurred within 12 hours in 75 (74.3%) women in the titrated oral group and 27 (25.5%) women in the vaginal group ($P < 0.01$; relative risk [RR] 8.44, 95% confidence interval [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 minute in the titrated oral group than in the vaginal group ($P < 0.01$; RR 0.10, 95% CI 0.01– 0.76). The conclusion is 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.

7.2 The efficacy of titrated oral misoprostol for labor augmentation

There is another randomized controlled trial to compare titrated oral misoprostol with intravenous oxytocin for labor augmentation at 36 to 42 weeks of gestation with

spontaneous onset of active labor (Ho et al. 2010). Women meeting the general selection criteria with regular contractions and an effaced cervix dilated between 3 and 9 cm, and who had inadequate uterine contractions (two or fewer contractions every 10 minutes) during the first stage of labor, were randomly assigned to titrated oral misoprostol or intravenous oxytocin. Augmentation–to–vaginal delivery interval and vaginal delivery within 12 or 24 hours were the primary outcomes. The data were analyzed by intention-to-treat. Of the 231 women, 118 (51.1%) were randomized to titrated oral misoprostol and 113 (48.9%) to titrated intravenous oxytocin. The median interval from the start of augmentation to vaginal delivery was 5.22 hours (3.77– 8.58 hours, 25th–75th percentile) in the misoprostol group, and 5.20 hours (3.23– 6.50 hours, 25th– 75th percentile) in the intravenous oxytocin group (P=.019). Complete vaginal delivery occurred within 12 hours for 92 (78.0%) women in the misoprostol group and for 97 (85.8%) women in the oxytocin group (P=.121; RR 0.91, 95% CI 0.80 –1.03). There were no significant differences between the two groups who delivered vaginally within 24 hours. Twelve (10.2%) women in the misoprostol group and 13 (11.5%) women in the oxytocin group underwent cesarean deliveries (P=.744; RR 0.88, 95% CI 0.42–1.85). Side effects and neonatal outcomes also did not differ between the two groups. The conclusion is that labor augmentation with titrated oral misoprostol or intravenous oxytocin resulted in similar rates of vaginal delivery within 12 and 24 hours.

7.3 The efficacy of hourly oral misoprostol for terminating midtrimester pregnancies

In addition, there was one pilot study of hourly oral misoprostol for terminating midtrimester pregnancies (Cheng et al. 2010b). 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 mcg/hr for the first 12 hours and 400 mcg/hr after 12 hours until delivery. Data including the induction-to-delivery interval and total dosage of misoprostol were recorded and analyzed. All 16 women successfully underwent vaginal termination within 36 hours. The median induction-todelivery 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 mcg. The most common side effect was diarrhea, which was easily relieved by medication. These preliminary results show that oral administration of misoprostol at hourly intervals is a promising method for terminating midtrimester pregnancies.

7.4 The outcomes of labor induction with titrated oral misoprostol between nulliparous and multiparous women

There was one retrospective study to review the medical records of all patients between 37 and 42 weeks of gestation with a Bishop score $\leqq$6 who underwent labor induction with titrated oral misoprostol solution (Cheng et al. 2010a). The women were allocated into two groups: nulliparous and multiparous. The women received one basal unit of misoprostol solution (20 ml, 1 mcg/ml) every hour for four doses; additional doses were titrated against individual uterine response. The interval of latent and active phase and vaginal delivery within 12 hours were the primary outcomes. Of the 112 women included in the study, 49 (43.8%) mulliparae and 63 (56.2%) multiparae underwent labor induction with titrated oral misoprostol solution. Although fewer women delivered vaginally within 12 hours 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 two groups regarding vaginal delivery within 24 hours (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%) women in the muliparous group underwent caesarean deliveries (P=0.02; RR 1.09; 95% CI 1.00–1.18). All induction intervals, 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 were no instances of hyperstimulation, which was defined as tachysystole or hypertonus with nonreassuring fetal heart rate pattern, although tachysystole defined as the presence of at least six contractions in 10 min over at least two 10-min windows, occurred in four (8.2%) nulliparous women and in four (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 an Apgar score of < 7 at 1 min. The conclusion is that titrated oral misoprostol solution is a promising method of labor induction for both nulliparous and multiparous women.

8. Adverse effects of misoprostol

In published case reports (Graber &Meier 1991; Bond &Van Zee 1994; Austin et al. 1997), accidental overdosing with misoprostol resulting in pyrexia, hypoxia, and rhabdomyolysis all occurred with a single intake at a dosage exceeding 3,000 μg. Therefore, these adverse effects are the sign of misoprostol toxicity, which is good indicator when administrating hourly oral misoprostol for terminating midtrimester pregnancies. The other common side effect is the nausea, vomiting or diarrhea. Although it commonly occurs in the course of hourly oral misoprostol for terminating midtrimester pregnancies, it rarely occurs in the course of labor induction or augmentation with titrated oral misoprostol. Furthermore, these side effects are easily relieved by medication.

9. Teratogenicity of misoprostol

A form of congenital facial paralysis known as Mobius syndrome and limb defects have occurred in the infants of women who have taken misoprostol during the first trimester for abortions which failed (Gonzalez et al. 1998; Pastuszak et al. 1998). First trimester exposure to misoprostol is also associated with high incidences of vascular disruption defects in newborns (Vargas et al. 2000). In the Latina American Collaborative Study of Congenital Malformations of 4673 malformed infants and 4980 control infants, an increased frequency of transverse limb defects, ring-shaped constrictions of the extremities, arthrogryposis, hydrocephalus, holoprosencephaly, and bladder exstrophy, but not Mobius syndrome, was found in those infants exposed to misoprostol in utero (Orioli &Castilla 2000). There are no known reports of teratogenicity of misoprostol ingestion when taken after the first trimester.

10. Conclusion

Cesarean birth rates are greater than 20% in many developed countries (Betran et al. 2007). The main diagnosis contributing to the high rate in nulliparous women is dystocia or prolonged labor. Traditionally, a policy of vaginal dinoprostone under immature cervix or early amniotomy with oxytocin administration under mature cervix for the prevention of

delay in labor progress is associated with a modest reduction in the rate of cesarean births (O'Driscoll et al. 1984). However, the course of vaginal dinoprostone or misoprostol is tedious, and excessive uterine contractility resulting in fetal distress is always concerned during the oral or vaginal use of the fixed-dosage misoprostol. The oxytocin administration through the intravenous route needs to be under the control of an intravenous pump machine 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. Additionally, misoprostol offers several advantages over dinoprostone or oxytocin such as longer shelf life, stability at room temperature, and easy administration. It is an ideal alternative to traditional dinoprostone or oxytocin in labor induction or augmentation. In consideration of interindividual or intraindividual variation of drug response during the dosing course, it is reasonable that the titrated oral misoprostol solution replaces the fixed dosage misoprostol via vaginal or oral route in labor induction or augmentation. In aspect of completing vaginal delivery to reduce the cesarean rate, the use of titrated oral misoprostol is also superior to the traditional use of vaginal misoprostol from the above randomized controlled trial.

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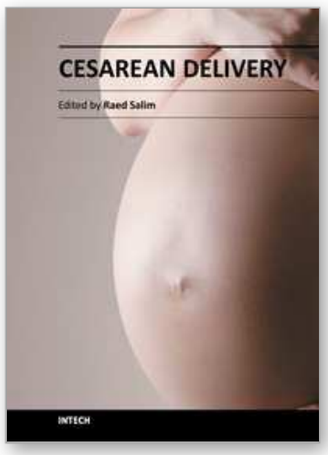

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This book provides broad, science-based information regarding the most common major surgical procedure performed, i.e. Cesarean Delivery. The book provides relevant scientific literature regarding epidemiology and rates of cesarean delivery in low and high income countries and the impact of the disparities in the rate of cesarean delivery between countries. In addition, the book systematically reviews the relevant scientific literature regarding all perioperative considerations with a broad cover of anesthetic techniques, drugs and difficulties that anesthesiologists may encounter during cesarean delivery. Care of the neonate after cesarean and crucial guidelines for obese women undergoing cesarean are also provided. The book was written by distinguished experts from different disciplines to ensure complete and accurate coverage of the recent scientific and clinical advances and to bring care providers and purchasers up to date including essential information to help improve health care quality.

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