Original Article

Effectiveness of Sequential Low Dose Oral Misoprostol Solution for Induction of Labor: An Experience in a Thai Quaternary Hospital

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Background: Siriraj Hospital has seen remarkably high cesarean section rates during the last decade. A labor induction protocol has been established to reduce cesarean section rate from "failed induction".

Objective: To determine effectiveness of a sequential low dose misoprostol solution protocol for labor induction. Cervical ripening and vaginal delivery rates, pregnancy outcomes, and associated factors of successful vaginal delivery were determined.

Materials and Methods: The present study was a retrospective observational study. Medical records of women with a term singleton pregnancy and with Bishop score of 6 or less who underwent labor induction were reviewed. The induction protocol started with series 1 which was 25 mL oral misoprostol solution (1 mcg/mL) every two hours for a maximum of 24 hours. If Bishop score was 6 or less by the end of series 1, then series 2 would follow, comprising 50 mL oral misoprostol solution (1 mcg/mL) every four hours for a maximum of 24 hours. Data of Bishop scores, delivery route by the end of each series, pregnancy outcomes, and possible associated factors were collected.

Results: One hundred twenty-eight women were analyzed. The overall rate of cervical ripening, with a Bishop score of more than 6, was 92.2%, and at 88.3% with series 1 only. Successful vaginal delivery was achieved in 70 cases (54.7%), 53 of whom were delivered within 24 hours. Significantly associated factors with successful vaginal delivery were multiparity, and birth weight of 3,200 grams or less; adjusted OR 4.0 (95% CI 1.31 to 12.16, p=0.015) and 3.4 (95% CI 1.48 to 7.63, p=0.004), respectively. No serious adverse pregnancy outcomes were observed.

Conclusion: With Siriraj induction protocol, success rates of cervical ripening and vaginal delivery were 92.2% and 54.7%, respectively, without serious adverse outcomes. Significant associated factors of successful vaginal delivery were multiparity and birth weight of 3,200 grams or less.

Keywords: Oral misoprostol, Misoprostol solution, Low dose, Labor induction, Cervical ripenting, Vaginal delivery

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Induction of labor is an intervention to unnaturally initiate labor with the aim for delivery, usually via starting uterine contractions[1]. It is performed if the benefits outweigh the risks, balancing against continuation of pregnancy. Maternal complications such as hypertension, diabetes, malignancy that needs urgent treatment, and some fetal conditions may warrant delivery. According to recent data, gestational age of 41 complete weeks or more increases incidence of birth asphyxia and stillbirth[2]. Timely delivery can ameliorate adverse outcomes[3]. Induction of labor would be useful when the pregnancy should be terminated but the labor does not commence spontaneously.

Siriraj Hospital is a tertiary and a university hospital in Thailand, with approximately 8,000 deliveries annually. During the last decade, remarkably high cesarean rates have been observed, for example the rate was 48.4% (3,807 cases) in 2017. One component of cesarean deliveries has been due to "failed induction". Although this indication presents a small proportion of the total cesarean number, an improved rate of successful induction should help such cases to avoid possible serious operation-related morbidities. In 2017, only 31% of women who were induced with an initial Bishop scores of 6 or less were able to deliver vaginally. Various labor induction protocols used by different staff members had been observed, the majority of which were oxytocin

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induction. Prostaglandins were rarely used due to concern of uterine hyperstimulation and its sequelae. Nevertheless, it occurred to the quality improvement team that a more reliable scheme for labor induction should be established to increase vaginal delivery rate in women with an unripe cervix who require labor induction.

Initiation of normal parturition is a result of hormonal changes involving estrogen, progesterone, and prostaglandins, followed by cervical ripeness, uterine contractions, and normal delivery[1]. The process can take several days to weeks. Induction of labor starts the parturition earlier rather than awaiting the labor to begin spontaneously. Dinoprostone, a prostaglandins E2, has been approved by the Food and Drug Administration (FDA) as a standard medication for labor induction[4]. Misoprostol, a synthetic prostaglandin E1 analogue, was developed to treat peptic ulcer. Owing to its side effects of stimulating uterine contractions and causing cervical ripeness, it has been applied for induction of labor[5]. Misoprostol is inexpensive, can be kept at room temperature, and can be administered in various routes[6]. Misoprostol comes in 100-, 200-mcg tablets. Due to concerns of uterine hyperstimulation, low doses of 20 to 50 mcg at frequent intervals had been pilot studied by Hofmeyr et al[7]. They also tried dissolving misoprostol tablet (200 mcg) in 200 mL water for accurate individual doses rather than breaking the tablet (25 mcg being equivalent to 1/8 tablet). Later, with a multicenter study, Hofmeyr et al found that the use of oral misoprostol had comparable outcomes as vaginal dinoprostone[8]. In their study, failure rate of vaginal delivery, and incidence of adverse effects such as tachysystole were 38% versus 36% and 4% versus 3% with misoprostol and dinoprostone, respectively. Results from a systematic review revealed that vaginal misoprostol and low-dose oral misoprostol had similar efficacy with a lower rate of uterine tachysystole in low-dose oral route[9]. A recent meta-analysis compared outcomes using Foley catheter, misoprostol via oral or vaginal route, and dinoprostone for induction of labor[10]. The lowest rate of vaginal delivery not achieved within 24 hours (30.2%) was found with vaginal misoprostol and the lowest cesarean delivery rate (20.7%) was found with oral misoprostol. Vaginal misoprostol had the highest rate of uterine hyperstimulation (6.1%) while oral misoprostol had the hyperstimulation rate of 2.1%. The oral route has additional advantages that it is easier to administer and more acceptable.

In 2017, the authors developed a protocol for induction of labor using low dose misoprostol solution with the aim to increase vaginal delivery rate among singleton pregnancies undergoing labor induction. The protocol has been launched in July 2018. It is described in detail in the following Materials and Methods section. The objective of the retrospective study was to determine the effectiveness of this protocol.

Materials and Methods

The present study was approved by the Siriraj Institution Review Board [229/2562 (EC4)]. Medical records of cases with labor induction between July 2018 and July 2019 were reviewed.

Inclusion criteria were pregnant women 18 years or older with a term singleton pregnancy admitted for induction of labor. Exclusion criteria included cases with rupture of membranes, fetal anomaly, stillbirth or intrauterine fetal death, and initial Bishop score greater than 6.

The induction protocol consisted of the following steps:

1. Oral misoprostol solution was prepared from a 200-mcg misoprostol tablet dissolved in 200 mL drinking water.

2. The protocol was started with series 1: oral misoprostol solution 25 mL (25 mcg) every two hours for a maximum of 24 hours (12 doses), and if Bishop score was still 6 or less, then series 2 would follow, which was oral misoprostol solution 50 mL (50 mcg) every four hours for a maximum of 24 hours (6 doses). The solution was stirred well before given.

3. Bishop score was assessed every four hours. The protocol was discontinued when Bishop score was greater than 6, which would not need any more cervical ripening[11]. Then, after at least four hours from the last dose of misoprostol, other methods were considered for augmentation of labor if needed. These included oxytocin infusion, amniotomy, or combination of both.

4. Continuous cardiotocography and monitoring of maternal vital signs were performed 30 minutes before and after each misoprostol administration. If non-reassuring fetal heart rate pattern, maternal hemodynamic instability, or uterine tachysystole with more than five contractions in 10 minutes occurred, the next dose of misoprostol would be postponed and immediate management such as intrauterine fetal resuscitation or tocolytic drug administration was given as appropriate.

Based on the prior study, success rate of vaginal delivery after induction of labor using oral misoprostol

was 62%[8]. The sample size was calculated by using 95% confidence interval (CI) with acceptable error of 0.09. The sample size was 105. With 20% attrition for incompleteness of data in the medical records, the sample size was 126 cases.

Collected data included age, gestational age, parity, body mass index (BMI), pregnancy complications, Bishop score before induction of labor, indication for induction, Bishop scores by the end of series 1 and series 2, route of delivery, estimated blood loss, birth weight, and Apgar scores. Statistical analysis was performed with IBM SPSS Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA) licensed by Mahidol University.

Failed induction was defined as inability to obtain cervical dilatation of at least 4 cm after 12 hours of good uterine contractions or augmentation[12].

The study primary objective was to determine vaginal delivery rate from this induction protocol. Secondary objectives were to determine associated factors of successful vaginal delivery using factors identified from univariate analysis for subsequent multivariate logistic regression analysis; and to determine pregnancy outcomes with this protocol. Additionally, cervical ripening rate, defined as Bishop score greater than 6, was also determined.

Results

One hundred sixty-eight women were admitted for induction of labor with the initial Bishop score of 6 or less. Forty cases were excluded from the study due to the following reasons, preterm (n=10), using other protocols (n=20), dead fetus in utero (n=5), rupture of membranes (n=3), and incomplete data (n=2). Finally, 128 cases were included whose demographic data are shown in Table 1. Although the mean BMI was 29.8, more than half of the women were within normal weight range. Mean gestational age on admission was 40.0±1.2 weeks. Eighty-two percent were nulliparous, and half of the cohort had a low Bishop score.

Figure 1 shows the protocol's performance in terms of cervical ripening and vaginal delivery rates. During series 1, cervical ripening could be accomplished in 113 women (88.3%). Fifty-three women (41.4% of the study population) succeeded in vaginal delivery, while 24 women (18.8%) underwent cesarean section. Women who delivered were not entirely the same as women with a ripe cervix. Some women who had a ripe cervix went into labor and delivered on the second day while some women with an unripe cervix underwent cesarean delivery within the first 24 hours. In the next 24 hours, five more women accomplished cervical ripening, 15 more achieved vaginal delivery, and 29 more had cesarean delivery. By the end of the protocol, which was 48 hours after induction, seven women (5.5%) remained undelivered. Subsequently two women were able to give birth vaginally without any adverse incident at 48 hours 30 minutes and 53 hours after commencing induction. The remaining five needed cesarean section due to cephalopelvic disproportion in three cases, non-reassuring fetal heart rate in one case, and failed induction in one case. The longest induction to delivery time of these cases was 54 hours. In summary, cervical ripening and vaginal delivery were achieved in 92.2% and 54.7% of the women, respectively. The majority of the two events occurred within the first day.

Table 1. Characteristic of study population (n=128)

	n (%)
Age (year); mean±SD	31.5±5.8
BMI (kg/m^2); mean±SD	29.8±5.9
GA on admission; mean±SD	40.0±1.2
Gestational weight gain (kg); mean±SD	14.0±6.3
Parity	
0	105 (82.0)
1	15 (11.7)
≥2	8 (6.3)
BMI (kg/m^2)	
Underweight	13 (10.2)
Normal weight	74 (57.8)
Overweight	24 (18.7)
Obese	17 (13.3)
Bishop score on admission	
≤3	70 (54.7)
>3	58 (45.3)
Indication of induction of labor	
Elective	58 (45.3)
Maternal indication	34 (26.6)
Fetal indication	31 (24.2)
Both maternal and fetal indication	5 (3.9)
Pregnancy complication	
None	84 (65.6)
DM	13 (10.2)
HT	20 (15.6)
Both DM and HT	9 (7.0)
Others	2 (1.6)

BMI=body mass index; GA=gestational age; DM=diabetes mellitus; HT=hypertensive disorder in pregnancy; SD=standard deviation

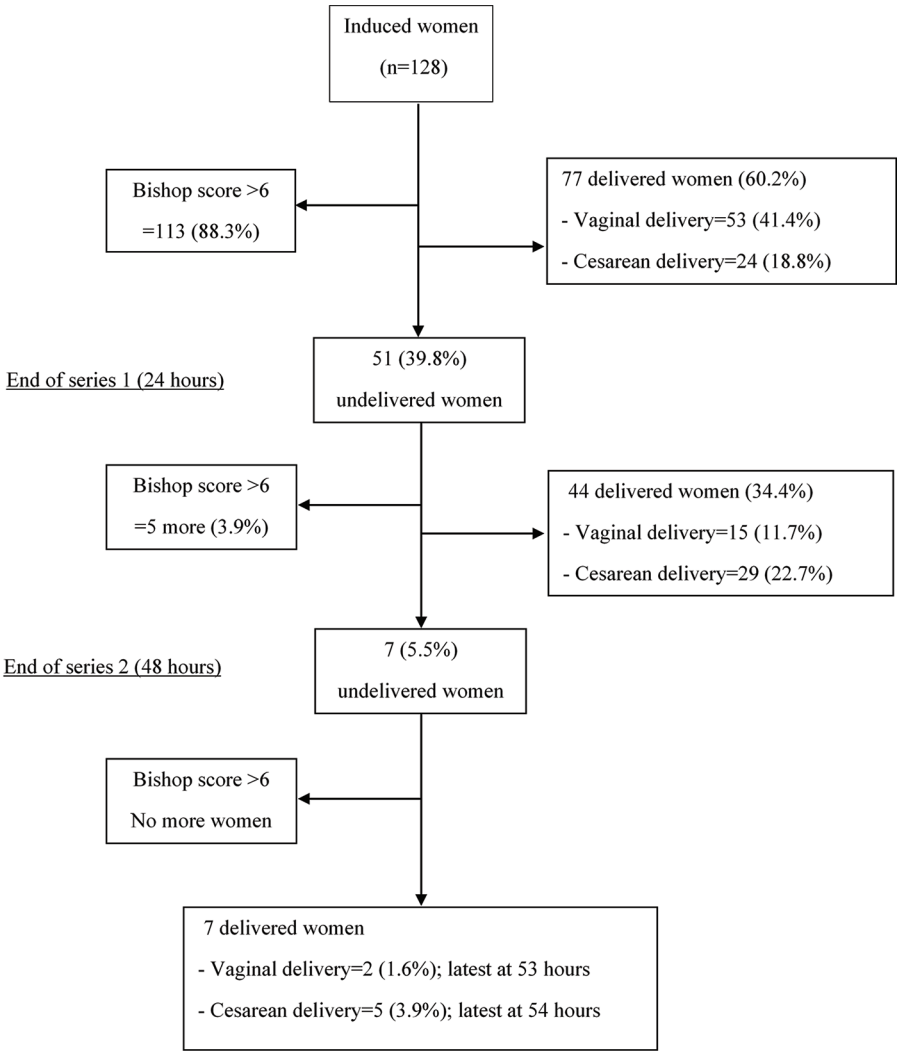

Figure 1. Result of labor induction.

Series 1: oral misoprostol 25 mcg every 2 hours maximum 12 doses; Series 2: oral misoprostol 50 mcg every 4 hours maximum 6 doses
%=percentage of the total study population (128 women)

The authors investigated the delivery route with the time lapse from starting induction in more detail. Figure 2 illustrates the number of women delivered by each route as time passed. The chance of vaginal delivery was apparently higher than cesarean section during the first 24 hours and then dropped visibly later. Receiver operating characteristic curve with an area under the curve of 0.657 (p=0.002) revealed that vaginal delivery was more likely to be achieved than cesarean delivery within the first 25 hours 30 minutes. Of 70 women who could delivered vaginally, 56 (80%) did so within this cut off value. They comprised 68.3% of 82 women who delivered within this period. When induction process took longer than 25 hours 30 minutes, the chance of the women to give birth vaginally was 30.4% with 14 out of 46 cases, or 11% of the entire cohort. The mean and median times to delivery in the vaginal group were 20 hours and 19 hours while those in the cesarean group were 27 hours and 28 hours, respectively.

Pregnancy outcomes of the women are shown in Table 2. Cesarean section rate was 45.3% with 58 cases. The most common indication for cesarean deliveries (43.1%) was cephalopelvic disproportion, while the second most common (34.5%) was failed induction. The remaining indications were non-reassuring fetal status, and maternal complications that needed urgent deliveries. Some women had more

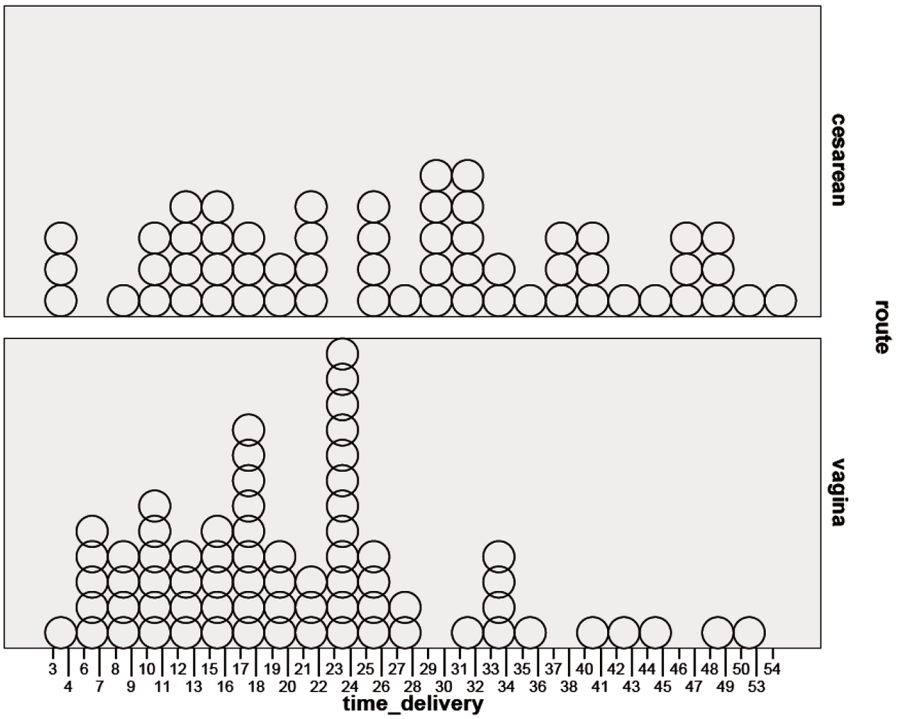

Figure 2. Number of women with route of delivery as function of time.

○=each woman

Table 2. Pregnancy outcomes of study population (n=128)

	n (%)
Route of delivery	
Normal vaginal delivery	70 (54.7)
Cesarean delivery	58 (45.3)
Indication for cesarean delivery (n=58)*	
Cephalopelvic disproportion	25/58 (43.1)
Failed induction of labor	20/58 (34.5)
Non-reassuring FHR/NICHD cat II	12/58 (20.6)
Preeclamsia/HELLP	5/58 (8.6)
Thick meconium stained amniotic fluid	3/58 (5.2)
Postpartum hemorrhage	12 (9.4)
Neonatal outcomes	
Birth weight (g); mean±SD	3,165±463
Birth asphyxia (Apgar score <7 at 5 minute)	0 (0.0)

FHR=fetal heart rate; NICHD cat II=the National Child Health and Humen Development category II; HELLP=hemolysis, elevated liver enzymes, and low plateletcount sydrome; SD=standard deviation

* Some women had more than one indication for cesarean delivery

than one indication. Postpartum hemorrhage, defined in the present study as blood loss greater than 500 mL after vaginal delivery or greater than 1,000 mL after cesarean delivery[13], was found in 12 cases (9.4%). No operative treatment was needed in these women. As for neonatal outcomes, the mean birth weight was 3,165±493 g. None of the infants had Apgar score of less than 7 at 5 minutes.

Table 3 shows the factors associated with route of delivery. Successful vaginal delivery was associated significantly with multiparity (OR 3.7, 95% CI 1.269 to 10.613, p=0.012), and birth weight of 3,200 g or less (OR 3.6, 95% CI 1.692 to 7.726, p=0.001). Multivariate analysis confirmed these two factors to be significantly associated with successful vaginal delivery with adjusted OR of 4.0 (95% CI 1.31 to 12.16, p=0.015) and 3.4 (95% CI 1.48 to 7.63, p=0.004), respectively (Table 4).

Discussion

The aim of the present study was to determine the performance of a labor induction protocol recently launched in Siriraj Hospital. The protocol had been set up to reduce cesarean rate in women with labor induction. The overall performance, especially success rate of vaginal delivery and the associated factors, were evaluated.

The results revealed that the protocol had a

Table 3. Factors associated with route of delivery (n=128)

Factors	Route of delivery; n (%)		OR	95% CI	p-value
	Vaginal delivery (n=70)	Cesarean delivery (n=58)			
Age (year)					
<35	49 (53.8)	42 (46.2)			
≥35	21 (56.8)	16 (43.2)	1.1	0.521 to 2.430	0.764
Parity					
0	52 (49.5)	53 (50.5)			
≥1	18 (78.3)	5 (21.7)	3.7	1.269 to 10.613	0.012*
BMI (kg/m^2)					
≤24.9	17 (70.8)	7 (29.2)	0.4	0.164 to 1.118	0.078
>24.9	53 (51.0)	51 (49.0)			
Bishop score on admission					
≤3	34 (48.6)	36 (51.4)			
>3	36 (62.1)	22 (37.9)	1.7	0.854 to 3.516	0.127
Birth weight (g)					
≤3,200	54 (65.9)	28 (34.1)	3.6	1.692 to 7.726	0.001*
>3,200	16 (34.8)	30 (65.2)			
Indication of induction of labor					
Elective	33 (56.9)	25 (43.1)			
Non-elective	37 (52.9)	33 (47.1)	1.2	0.585 to 2.371	0.648
Pregnancy complication					
DM	9 (40.9)	13 (59.1)	0.5	0.201 to 1.298	0.154
Non-DM	61 (57.5)	45 (42.5)			

BMI=body mass index; DM=diabetes mellitus; OR=odds ratio; CI=confidence interval

* Statistical significant (p<0.05)

Table 4. Multivariate analysis of factors associated with route of delivery (n=128)

Factors	Route of delivery; n (%)		OR_{adj}	95% CI	p-value
	Vaginal delivery (n=70)	Cesarean delivery (n=58)			
Parity ≥1	18 (78.3)	5 (21.7)	4.0	1.31 to 12.16	0.015*
BW ≤3,200 g	54 (65.9)	28 (34.1)	3.4	1.48 to 7.63	0.004*

BW=birth weight; OR_{adj}=adjusted odds ratio; CI=confidence interval

* Statistical significant (p<0.05)

high success rate of cervical ripening (92.2%). Disappointingly, vaginal delivery rate was achieved in only 54.7%. This was similar to the study of Pimentel et al, which reported that successful vaginal delivery rate was 52.0%[14]. Higher vaginal delivery rates after oral misoprostol induction were reported by Rouzi et al[15] (65.8%) and Ngai et al[16] (76%). The different results may be due to higher cumulative dose and higher number of multiparity in the study of Rouzi et al[15] and inclusion of cases with premature rupture of membranes in that of Ngai et al[16].

Although previous studies[17,18] showed that there were several factors associated with successful vaginal delivery such as Bishop score, parity, BMI, maternal morbidity, gestational age, maternal age, and fetal weight, the present study showed only two significant factors, which were multiparity and birth weight of 3,200 g or less. Similarly, Gibson et al found that in elective induction, multiparous women had a higher vaginal delivery rate than nulliparous women[19]. Melamed et al used prostaglandin E2 for induction in a smaller sample size population with 88 cases[20]. They found that associated factors with induction failure included nulliparity, pre-pregnancy

BMI greater than 25 kg/m², and Bishop score on admission of less than 4. Vrouenraets et al found that Bishop score of less than 5 was associated with cesarean section in nulliparous women, irrespective of whether the labor was induced or spontaneous[21]. As the authors included only women with Bishop score of 6 or less, the women could only be divided into Bishop score of 0 to 3 and 4 to 6. The difference in the delivery route between such close and narrow ranges of scores might not be discernable.

As misoprostol can cause uterine tachysystole and decreases uteroplacental blood flow, close observation by continuous electronic fetal monitoring before and after drug administration are recommended. The administered dose should be as low as possible while keeping the efficiency of labor induction. A Cochrane review found that cesarean rates between using oral misoprostol 25 mcg versus 50 mcg regimens were not significantly different (RR 0.94, 95% CI 0.33 to 2.68)[22]. Siriraj protocol was thus developed starting with 25 mcg per dose[23] and was designed to comprise two sequential series, increasing to 50 mcg per dose if needed with longer intervals.

The present study protocol was slightly similar to that of Morris et al[24] in terms of sequential nature of medication given. In their protocol, misoprostol 25 mcg was given orally every two hours for a maximum of four doses and increased to 50 mcg every two hours for a maximum of eight doses. Then, if no labor pursued, the woman was rested for 24 hours after which 50 mcg misoprostol solution was given every two hours for a maximum of eight doses. Finally, if the cervix was still not favorable, Foley catheter induction or cesarean section was considered. Their result showed much higher vaginal delivery rate than the present study (188/209; 90%). Seventy-four percent of the vaginal deliveries took place within 24 hours after induction. Their higher success rate in vaginal delivery may be due to their study population. They did not exclude preterm, premature rupture of membranes, and dead fetus in utero from the study. In addition, women in their study received a higher amount of misoprostol than in the present study. As for neonatal outcomes, 10 neonates in their study had an Apgar score of less than 7 at 5 minutes compared with none in the present study protocol.

All in all, the current protocol could increase vaginal delivery rate in women with an unripe cervix who require labor induction. As mentioned, the vaginal delivery rate in such women in the authors institution had been 31% in 2017 when only oxytocin was the preferred method of induction owing to concerns of uterine tachysystole caused by prostaglandins. With this protocol, the vaginal delivery rate increased to 54.7%. Misoprostol helps cervical ripening, rendering the cervix to be ready for further effacement and dilatation, improving success rate of labor induction and vaginal delivery. In addition, the diagnosis of "failed induction" was more stringent than it had been in the past. Decision for abdominal delivery was made with more consideration. From the study result, women could be counseled that safe vaginal delivery after 24 hours of induction can still be accomplished in more than 10% of women with unfavorable cervix. Vaginal delivery could be expected in about two third of deliveries in the first 25 hours and approximately 30% of deliveries afterward. This information might help alleviate their anxiety.

The present study was performed on women with a term singleton pregnancy, with an unripe cervix and without rupture of membranes. Possible effect on cervical ripening from intrauterine fetal death, or certain fetal anomalies was excluded. Therefore, the study gives insight on effect of low dose misoprostol solution per se on cervical ripening. The success rate of vaginal delivery was also determined simultaneously. As the protocol had been launched as the departmental policy and the criteria for the diagnosis of "failed induction" had been set, such diagnosis was carried out in the same manner among staff members. Generally, the issue is still problematic as admitted by several authors[18,25,26].

However, study limitations have been appreciated. Firstly, diagnosis of "cephalopelvic disproportion" was imprecise as it depended on judgement of the staff on duty. In addition, variation existed in threshold for decision making in certain situations such as preeclampsia, oligohydramnios, or non-reassuring fetal status diagnosed from electronic fetal monitoring. Explicit criteria to diagnose these situations may help reduce cesarean rate further. Secondly, at the early period of the protocol launch, several cases were not yet managed accordingly. Twenty women had to be excluded from the study. This might have possibly caused a selection bias. From a previous study, maternal morbid obesity and large for gestational age have been found to be associated with an increased cesarean delivery rate[27,28]. Since the present study population had only a few cases with morbid obesity or a large for gestational age fetus, such association could not be determined. Lastly, as a university hospital, cervical assessment was performed by various levels of residents and staff members thus it might be somewhat confounded.

Modification of the protocol with frequent administration of misoprostol only during daytime for more convenience and acceptance is underway in the authors' institution. If the performance was comparable, then this modification would be more suitable.

Conclusion

Regarding sequential small-dose misoprostol solution protocol, the success rate of cervical ripening according to the Bishop score of greater than 6 was very high at 92.2%, and success rate of vaginal delivery was moderate at 54%. Significant associated factors of successful vaginal delivery were multiparity and birth weight of 3,200 g or less.

What is already known on this topic?

Oral misoprostol has been used for labor induction usually within 24 hours only or with a pause in between resulting in a long period of induction time or a high rate of failed induction.

What this study adds?

Oral misoprostol solution given in small frequent doses during the first 24 hours and increased to a larger dose with less frequency in stepwise fashion during the next 24 hours under close maternal and fetal monitoring before and after each dose can bring about a moderate successful vaginal delivery rate without harmful effects.

Conflicts of interest

The authors declare no conflicts of interest.

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