



## Misoprostol for Induction of Labor: A Review

Authors

**Mahajan M<sup>1</sup>, Gupta, KB<sup>2</sup>, Sharma, R<sup>3</sup>**

<sup>1</sup>M.S. (OBG) Government Civil Hospital, Theog, District Shimla, Himachal Pradesh

Email: [drmamtamahajan@gmail.com](mailto:drmamtamahajan@gmail.com)

<sup>2</sup>M.S. (OBG) Former Professor & Head, Kamla Nehru State Hospital for Mother & Child, Indira Gandhi Medical College, Shimla – 171002

<sup>3</sup>M.S. (OBG) Former Professor, Kamla Nehru State Hospital for Mother & Child, Indira Gandhi Medical College, Shimla – 171002

### Abstract

*Induction of labor is widely used across the globe in cases where continuing pregnancy is unsafe for the mother and/or her fetus. Numerous techniques are available for induction of labor. Use of misoprostol appears one of the effective methods of cervical ripening and labor induction. The effectiveness and safety of misoprostol administered vaginally or orally for labor induction have been reviewed in the present paper. Since the use of misoprostol can have maternal and perinatal implications, it is important to review the effectiveness of misoprostol in cervical priming and induction of labor. This paper reviews the effectiveness and safety of misoprostol administered orally, sublingually and vaginally for induction of labor.*

**Keywords:** *Induction of labor, Misoprostol, oral administration, vaginal, sublingual*

### 1. Introduction

Labor is a process through which the fetus moves from the intrauterine to the extra-uterine environment. In clinical terminology, labor is defined as the initiation and perpetuation of uterine contractions with the goal of producing progressive cervical effacement and dilation. Induction of labor (IOL) refers to the process whereby uterine contractions are initiated by medical or surgical means before the onset of spontaneous labor<sup>[1]</sup>. IOL has been of interest to many societies, from the primitive to the contemporary times. A number of folkloric or old midwives tales are still used today by the women to encourage their labor to start.

Among the common approaches are frequent walking, vaginal intercourse, participating in heavy exercise, consumption of laxatives, spicy foods or herbal tea, nipple stimulation and administration of enema<sup>[2]</sup>. Chemical methods of labor induction used by Native Americans included the administration of powdered rattle of rattle snakes in a potion. Another potion was derived from bear claw scrapings. Hippocrates recommended nipple stimulation as one of the methods of labor induction which would lead to uterine contractions<sup>[3]</sup>. In 1756, a meeting of most distinguished Obstetricians in London concluded that labor can be induced by rupturing the membranes of woman with small pelvis, which was formally adopted by a British Physician, Dr.

Thomas Denman and referred to as English method. In 1810, Professor James Hamilton suggested digital separation of membranes from the lower uterine segment and then rupturing the membranes above the fetal head, i.e., high rupture. Sponges, enemas, rupturing of membranes, and venesection continued till late 19<sup>th</sup> century. In late 19<sup>th</sup> century and early 20<sup>th</sup> century, cervical dilatation continued to be much in vogue. Krause's method introduced in 1853 involving the insertion of the bougie between the membranes and the uterine wall remained in trend for many years<sup>[4]</sup>. 'Colpeurytnar' a balloon developed by De Lee, which was a modification of Boissard balloon was first introduced in 1894 in France. At a time when aseptic technique was not the best and when antibiotics were non-existent, many of these invasive procedures were morbid for both the patient and infant. In early 20<sup>th</sup> century, ergot, quinine and pituitary extract became the primary medication of labor induction. In 1909, William Blair Bell started using pituitary extract to initiate and augment labor. By 1922, quinine and pituitary extract were recognized as labor inductants. In 1969, chemists at Upjohn Pharmaceuticals and Elias J. Corey with his colleagues at Harvard were able to synthesize prostaglandins and started the era of the use of prostaglandins in labor induction<sup>[3]</sup>. Later, numerous researchers and physicians experimented with newer methods of labor induction, for instance, Karim and Sharma in 1971 attempted labor induction with vaginal administration of prostaglandin and PGF<sub>2</sub> $\alpha$  and concluded that vaginal route of administering prostaglandin for termination of pregnancy was certainly more acceptable and practical than continuous intravenous infusion<sup>[5]</sup>. Nelson and Bryans in 1976 compared oral PGE<sub>2</sub> and intravenous oxytocin for IOL in normal and high risk pregnancies and concluded oral PGE<sub>2</sub> administration as safe and effective alternative to intravenous oxytocin for IOL in normal and high risk pregnancies<sup>[6]</sup>. Rajan *et al.* in 1983, conducted elective IOL by forewater amniotomy and discussed various factors that influenced the favorable

outcome of elective induction by this method<sup>[7]</sup>. Likewise, Johnson *et al.* in 1985, studied the efficiency of Lamichel, a synthetic cervical ripening agent, compared with those of intravaginal PGE<sub>2</sub> gel and concluded that Lamichel caused less uterine activity and fetal distress than prostaglandin gel, although induction to delivery intervals was similar in both the group<sup>[8]</sup>.

Rates of labor induction has increased significantly, which doubled from 9.5% in 1990 to almost a quarter of US pregnant women undergoing induction in 2012. In 2004 and 2005, one in every five deliveries in UK was induced. The rates of induction were at 23% in England, Scotland and Wales in 2012<sup>[9]</sup>. As the population of females undergoing induction grows, there is a constant search for more efficacious and easy to use inducing agent while maintaining fetal and maternal safety.

### **Misoprostol for Induction of Labor**

The use of misoprostol in pregnancy has been reviewed since long. In the present paper, an attempt has been made to review the evolution of misoprostol as a labor induction agent and to show how effective dose with minimal side effects have been evolved over the years. Misoprostol is synthetic prostaglandinE<sub>1</sub> analogue, that accelerates physiological cervical ripening and is an effective myometrial stimulant selectively binding to EP-3 prostanoid receptors. Danielsson *et al.*<sup>[10]</sup> (1999), found that after vaginal administration, but not after oral administration, uterine activity increase continuously for 4 hours. This might lead to cumulative effect with the subsequent dosing. Persistent increased uterine activity and possible cumulative effect might explain increased incidence of uterine activity with vaginally administered misoprostol tablets. It is extensively absorbed and undergoes rapid desaturation to its free acid which is responsible for clinical activity. It is rapidly absorbed after oral administration with T<sub>max</sub> of misoprostol acid of 12 $\pm$ 3 minutes and has a terminal half-life of 22-40 minutes. Thus, after oral administration it is characterized by short half-life<sup>[11]</sup>. It has been used for IOL through vaginal,

oral and sublingual routes. Most trials have studied vaginal route of administration for misoprostol in IOL.

Sanchez-Ramos, *et al.*<sup>[3]</sup>, 1993 and Fletcher in 1993<sup>[12]</sup> were the first to look at the use of vaginal misoprostol for IOL in a viable fetus at term, and the results were published in 1993. Since April 2002, misoprostol is legitimate part of the FDA – approved regime for use with Mifepristone to induce abortion in early pregnancy and is also recognized for its use for IOL.

Compared with placebo or expectant management, misoprostol is associated with a reduced risk of not achieving vaginal birth within 24 hours of induction with fewer caesarean section. Beigi *et al* 2003 determined efficacy of 200 µg of single dose of oral misoprostol as compared to Placebo. It was a double-blind randomized trial. 156 pregnant women were randomized to receive either 200 µg of misoprostol orally or placebo orally. The interval between oral medication and delivery was significantly shorter in misoprostol group ( $P < 0.001$ ) and also cesarean delivery rate was lower ( $P < 0.001$ ). They concluded that oral misoprostol is an effective agent not only for cervical priming but also for IOL at term. Furthermore, it reduces the rate of caesarean deliveries<sup>[13]</sup>.

Ramsey *et al.* in 2003 compared the efficacy and cost of prostaglandin analogs dinoprostone and misoprostol as labor pre-induction agents. 111 women with an unfavorable cervix who underwent labor induction were assigned randomly to receive either misoprostol 50 µg every 6 hours for 2 doses, dinoprostone gel 0.5 mg every 6 hours for 2 doses, or dinoprostone insert 10 mg for 1 dose intravaginally. 12 hours later, Oxytocin induction was initiated per standardized protocol. Results showed that the mean Bishop Score change over the initial 12 hour interval was significantly greater in the misoprostol group ( $5.2 \pm 3.1$ ) compared with dinoprostone insert ( $3.2 \pm 2.3$ ) or dinoprostone gel groups ( $2.2 \pm 1.3$ ,  $p < 0.0001$ ). Induction-to-delivery interval were significantly shorter among women who were treated with misoprostol ( $24.0 \pm 10.8$  hours) compared with either dinoprostone gel

( $31.6 \pm 13.4$  hours) or dinoprostone insert ( $32.2 \pm 14.7$  hours;  $P < 0.05$ ). No significant difference was noted in the study with respect to mode of delivery or to the adverse maternal/neonatal outcome<sup>[14]</sup>.

Langenegger *et al.* 2004 compared the oral misoprostol with dinoprostone for IOL and their effects on the fetal heart rate patterns. In a randomized controlled trial, 200 patients were administered 50 µg misoprostol orally for every 4 hours or dinoprostone 0.5 mg intra-cervically for every 6 hours. No significant differences were observed in respect of the number of vaginal deliveries within 24 hours (RR 1.12; 95% CI 0.88-1.42). The study concluded that oral misoprostol is as effective as intracervical dinoprostone for IOL with no difference in the frequency of fetal heart rate abnormalities<sup>[15]</sup>. Considering the comparable efficacy of misoprostol and PgE<sub>2</sub> gel, comparable side effects and neonatal outcome with the advantage of being stable at room temperature is inexpensive and readily accessible makes misoprostol a better alternative to PgE<sub>2</sub> gel for IOL. Women induced with Misoprostol have reduced need for augmentation of labor, lower cesarean section rate and shorter induction to delivery interval (Table 1).

**Table 1:** Comparison of misoprostol with other labor inducing agents

Author	Study	Aug. Oxytocin	Caesarean Section Rate	Induction to Delivery Interval
Winget <i>et al.</i> 1995 [16]	Vaginal misoprostol 3 hourly Max 8 doses (138 women) Vs PgE <sub>2</sub> gel µg /6 hourly Max 3 doses(137women)	45%	CS=20.3%	1323=8444.4min
		72.6% (P<0.0001)	27.7%	1532.4=706.5min
Danielian, 1999 <i>et al.</i> [16]	Vaginal misoprostol 50 µg 4 hourly Max 4 doses (104 women) Vs PgE <sub>2</sub> gel 1 mg /6 hourly Max 3 doses(105 women)	21%	Similar in both groups	14.4 hours
		47% (P<0.0001)		22.9 hours
Bartha <i>et al.</i> 2000 [18]	Oral misoprostol 200 µg Single dose (100 women) Vs PgE <sub>2</sub> gel 0.5 mg /6 hourly Max 4 doses(100 women)	52%	1 % for failed induction	14 hours
		68%	9% for failed induction	20.2 hours
Shetty <i>et al.</i> 2004 [19]	Oral misoprostol 100 µg /4 hourly max=5 doses (100 women) Vs Prostaglandin E <sub>2</sub> 3mg/6 hourly (100 women)	60	V=46 ID=29 CS=25	28.03hrs
		47	V=47 ID=26 CS=27	29hrs
Gemundet <i>et al.</i> 2004 [20]	Vaginal misoprostol 25 µg /4 hourly Max=3 dose daily(341 women) Vs Dinoprostone gel (1mg)/4 hourly	58%	V=68% CS=16%	25hrs
		45%	V=61% CS=21%	19hrs
Baruah <i>et al.</i> 2005 [21]	Vaginal misoprostol 50 µg /4 -6 hourly , max = 6 doses(100women) Vs Intracervical PgE <sub>2</sub> gel 0.5 – mg 6 hourly, max = 2 doses (100 women )	1.94=0.84SD	V=74 ID=15 CS=11	10.99 hrs = 4.03 SD
		1.56 = 0.5 SD	V=68 ID=14 CS=18	18.00 hrs = 2.0 SD
Mahajan <i>et al.</i> 2010 [22]	Sublingual misoprostol 25 µg/4 hourly Max 6 doses (50 Women) Vs PgE <sub>2</sub> Gel 0.5 mg 12 hourly max 2 doses (50 Women)	58%	V=86% ID=2% CS=12%	17.82 hrs ± 7.15
		78% P=0.032	V=70% ID=4% CS=26%	17.45 hrs ± 5.23

V= Vaginal, ID= Instrumental Delivery, CS= Cesarean Section

However, because of the risk of uterine hyper stimulation with vaginal misoprostol, recent trials take into account the lower vaginal misoprostol doses and oral route for misoprostol administration. Roux *et al.* (2002) evaluated the efficacy of oral and vaginal misoprostol and compared with standard regimen using dinoprostone for IOL. Patients admitted for IOL were randomized to receive oral

misoprostol (N=120), vaginal misoprostol (N=120) or the control, dinoprostone (N=240). 50 µg dose of misoprostol was given orally or vaginally at 6 hours intervals to maximum of 4 doses. PgE<sub>2</sub> gel was given as 1 mg dose in the posterior fornix every 6 hours (maximum of 2 doses). There was no significant difference in vaginal delivery rate in 24 hours between the vaginal misoprostol and

dinoprostone groups. However, significantly fewer women delivered vaginally in the oral misoprostol group as compared with those in dinoprostone group. The median induction to vaginal delivery time in vaginal misoprostol, oral misoprostol and PgE<sub>2</sub> gel group was 12 hours, 23 hours and 14 hours respectively. The cesarean rate was approximately 33% in all the groups. More cesareans were performed for fetal distress in vaginal misoprostol group as compared to dinoprostone group (relative risk 2.86, 99% confidence interval 1.49, 5.46). There was higher incidence of tachysystole in the vaginal misoprostol group (5.8%) as compared to other two groups, i.e. oral misoprostol (0.8%) and dinoprostone (0.8%). The study concluded that vaginal misoprostol is as effective as PgE<sub>2</sub> gel in IOL, but it is associated with more tachysystole and cesarean section for fetal distress as compared to dinoprostone. Oral misoprostol results in fewer vaginal deliveries in 24 hours but is not associated with increased tachysystole or fetal distress<sup>[23]</sup>.

Higher doses of Misoprostol leads to increased risk of uterine hyper stimulation, whereas risk of vaginal birth not being achieved in 24 hours is similar in both higher and lower dose groups. Garlan *et al* in 2001 used higher doses of misoprostol and there was higher incidence of hyper stimulation, tachysystole and cesarean section. He compared the safety and efficacy accompanying oral and vaginal misoprostol for cervical ripening. 1004 women for labor induction randomly assigned to receive oral (N=403) or vaginal (N=501) misoprostol. Initial doses of 200 µg oral and 50 µg of vaginal misoprostol were increased to 300 µg oral and 100 µg vaginal after 2 doses to a maximum of 6 doses. It was given every 6 hours in both the groups. Oral misoprostol was associated with significantly higher frequency of intervention (13.3% vs. 8.4%, P=0.01), Tachysystole (23.6% vs. 17.6%; p=0.02) and Hyperstimulation (18.6% vs. 13.7%, p=0.04). There was no significant difference in caesarean rates (29.2 % vs. 24%). Mean number of misoprostol doses used (1.5 vs. 1.6, p=0.18) or hours from drug administration to delivery (24.5 vs. 25.4, p=0.77) between the oral and vaginal groups respectively.

The number of deliveries between the groups within 24 hours was different to (271{56%} vs. 290 {60%}, p = 0.02), oral and vaginal respectively. No adverse neo-natal outcome was noted. It was thus found that oral misoprostol has similar efficacy as vaginal misoprostol but is associated with higher frequency of excessive uterine contractility and intervention at higher doses<sup>[24]</sup>.

Ramos *et al.* in 2002 compared the safety and efficacy of 25 µg vs 50 µg of intravaginal misoprostol for cervical ripening and labor induction by evaluating five randomized controlled trials which met the inclusion criteria for meta-analysis. Odds ratio (OR) with 95% confidence intervals (CI) were calculated for each outcome and the study indicates that intravaginal misoprostol at doses of 50 µg for cervical ripening and labor induction is more efficacious but it was unclear whether it was as safe as the 25 µg dose<sup>[25]</sup>.

Bartusevicius *et al.* in 2005 reviewed 17 studies on 3549 patients to evaluate the effectiveness and safety of different administration routes of misoprostol for IOL. He concluded that compared to vaginal administration, oral misoprostol was associated with higher failure rates for achieving vaginal delivery within 24 hour (OR 1.61, 95% CI, 1.23-2.10), higher rates of uterine hyper stimulation without fetal heart rate changes (OR 2.21, 95% CI, 1.12-4.34) and lower cesarean section rates (OR 0.74, 95% CI, 0.562-0.97). A lower dose of oral misoprostol (50 µg) compared to 25-50 µg administered vaginally was associated with a higher rate of vaginal delivery not being achieved within 24 hours (OR 3.60, 95% CI, 2.10-6.18). The results of literature review revealed doubling of oral dose or more increased rate of uterine hyper stimulation syndrome over 12 fold (from 1.8% to 21.9%) and uterine hyper stimulation without FHR changes was doubled (from 15.3% to 28.7%)<sup>[26]</sup>.

Vaginal misoprostol in its currently recommended dose of 25µg seems to be similar to 50µg of vaginal misoprostol. Furthermore, vaginal misoprostol in dosage 50µg was associated with three fold higher rate of uterine hyperstimulation syndrome (5.9% versus 1.8%) and near fivefold higher rate of uterine

hyperstimulation without FHR changes (17.1% versus 3.7%). Lokugamage *et al* 2003 compared the efficacy and safety of intra-vaginal misoprostol and intra-vaginal dinoprostone for labor induction and quantified the clinical response to suspicious cardiotocographic (CTG) readings. 191 patients were randomized to receive 50 µg misoprostol initially and further identical dose 6 hours later or 2 mg dinoprostone followed by 1 mg 6 hours later over a period of 24 hours. There was increase in median number of times, a doctor was called to advise on the suspicious CTG in misoprostol group (1 vs. 2 occasions,  $P=0.052$ ) but there was no difference in neo-natal outcome. The study concluded that intra vaginal misoprostol lead to a shorter but more efficient labor and although there was more anxiety related to the CTG, there was no increase in neonatal adverse effects<sup>[27]</sup>.

Wing *et al* in 1999 compared orally administered with vaginally administered misoprostol for cervical ripening and labor induction. 220 subjects were evaluated, 110 received orally administered misoprostol (50 µg every 4 hourly to a maximum of 6 doses) and 110 received vaginal misoprostol (25 µg every 4 hourly to maximum of 4 doses). Fewer subjects who received the oral preparation (34/110, 30.9%) delivered vaginally within 24 hours of initiation of induction in comparison with those who received the vaginal preparation (52/110, 47.3%) ( $p=0.1$ ). The average interval from start of induction to vaginal delivery was nearly 6 hours longer in the oral treatment group (mean and SD  $1737.9 \pm 845.7$  minutes) than in vaginal treatment group (Mean and SD  $1393.2 \pm 767.9$ ). Orally administered patients required significantly more doses than vaginally treated patients (orally administered doses Mean & SD  $3.3 \pm 1.7$ ; vaginally administered doses: Mean & SD  $2.3 \pm 1.2$ ) ( $p<0.0001$ ) oxytocin administration necessary in 75.4% of orally treated subjects and in 59.1% of vaginally treated subjects. Vaginal delivery occurred in 86.4% orally treated and 77.3% vaginally treated subjects, with the remainder undergoing cesarean delivery. There was no difference in the incidence of uterine contractile abnormalities, intra-partum complications or

neonatal outcomes between two groups. Thus, it was concluded that oral administration of 50 µg doses of misoprostol appears less effective than vaginal administration of 25 µg doses of misoprostol for cervical ripening and labor induction<sup>[28]</sup>.

Wing *et al.* in 2000 conducted a randomized comparison of oral and intravaginal misoprostol for labor induction. 236 women were randomly assigned to receive 100 µg of oral (N=121) or 25 µg of vaginal misoprostol (N=113) every 4 hours for 24 hours. Intravenous oxytocin was then given using a standardized protocol. The mean interval from start of induction was  $1240 \pm 845$  minutes for orally treated women and  $1381 \pm 802$  minutes for vaginally treated women ( $p=0.06$ ). More orally treated women delivered vaginally in 24 hours than vaginally treated women (74 vs. 54,  $p=0.14$ ). 106 women (87.6%) who received oral misoprostol delivered vaginally as compared 88 women (77.9%) who received vaginal misoprostol ( $p=0.07$ ). Oxytocin was given to 49.6% orally treated and 52.2% vaginally treated subjects ( $p=0.69$ ) more women in the oral group had tachysystole, 9 compared with 2 ( $p=0.06$ ), hypertonus and hyperstimulation. Frequencies of intrapartum complications and birth outcomes were similar in two groups. Thus, it was found that oral misoprostol 100 µg and vaginal misoprostol 25 µg were effective for cervical ripening and labor induction. Therefore, the dose of oral misoprostol must be higher than vaginal misoprostol in order to achieve similar effectiveness. But increasing the dose of misoprostol necessitates carefully balancing the benefit against the risk<sup>[29]</sup>.

Sublingual misoprostol was found to be more effective than vaginal misoprostol for reducing the risk of vaginal birth not achieved within 24 hours. Bartusevicius *et al.* 2006 compared the efficacy and safety of 50 µg of sublingual misoprostol with 25 µg of vaginal misoprostol administered for labor induction at term. 140 women were randomized to receive either 50 µg of sublingual misoprostol with vaginal placebo (n=70) or sublingual placebo with 25 µg of vaginal misoprostol (n=70) every 4 hours

(maximum 6 doses) 83% in sublingual group and 76% in vaginal group delivered vaginally within 24 hours interval. However, the induction to vaginal delivery time was significantly shorter in sublingual group ( $15 \pm 3.7$  hours) as compared to vaginal group ( $16.7 \pm 4.1$  hours,  $p=0.03$ )<sup>[30]</sup>.

Feitosa *et al* 2006 compared sublingual misoprostol with vaginal misoprostol for IOL in 150 women who received every 6 hour 25 µg of sublingual misoprostol and vaginal placebo or 25 µg of vaginal misoprostol and sublingual placebo. Maternal and neonatal outcomes were analyzed and risk ratios with 95% confidence intervals were calculated. The significant level was 5%. The study concluded that the administration of 25 µg of misoprostol by sublingual route was neither more effective nor safer than the same route administered vaginally<sup>[31]</sup>.

These studies indicate that vaginal and sublingual misoprostol are similar with regard to all the major outcomes as shown in Table 2.

Shetty *et al.* 2002 compared the efficacy and patient acceptability of 50 µg of sublingual misoprostol or 100 µg oral misoprostol in labor induction at term. 250 women at term with indication for labor induction were randomized to receive either 50 µg of sublingual misoprostol or 100 µg of oral misoprostol every 4 hours to maximum of 5 doses. The study indicated that there was no difference in uterine hyperstimulation rates (1.6%) in both the groups, operative delivery rates and neonatal outcomes. In the sublingual group, 92.6% found the induction acceptable with 15.8% finding the tablet with an unpleasant taste, while in oral group it was 96.9% and 4% respectively<sup>[32]</sup>.

**Table 2:** Studies indicating similar outcome in vaginal and sublingual misoprostol

Author	Study	%age of Women requiring Oxytocin	Mode of Delivery	Intra- Partum Complication	Fetal outcome
Bartusevicius <i>et al.</i> (2006) <sup>[30]</sup>	Sublingual misoprostol(50µg)	49%	V=76% ID= 7.1% CS=17%	Hypertonus=2.9% Tachysystole=14% Hyperstimulation=7.1% MSL=27%	Apgar score<7 at 5min=2.9% NICU admission=2.9%
	Vaginal misoprostol(25µg)	49%	V=77% ID= 2.9% CS=20%	Hypertonus= 4.3% Tachysystole= 4.3% Hyperstimulation=7.1% MSL=27%	Apgar score<7 at 5min =2.9% NICU admission=2.9%
Feitosa <i>et al.</i> (2006) <sup>[31]</sup>	Sublingual misoprostol(25µg)	35%	V=57% CS=43%	Hypertonus = - Tachysystole = 9% Hyperstimulation =4% MSL=16%	Apgar score<7 at 5min=0 NICU admission=1%
	Vaginal misoprostol (25 µg)	-	CS= 30% V=70 %	Hypertonus = - Tachysystole = 7% Hyperstimulation = 1% MSL=17%	Apgar Score < 7=-1 min. = 15% 5 min. = 3% NICU Admission = 1%

NICU= Neonatal Intensive Care Unit, V= Vaginal, ID= Instrumental Delivery, CS= Cesarean Section

Shetty *et al.* in 2002 evaluated the efficacy, safety and patient acceptability of sublingual misoprostol and compared with an equivalent dose administered orally for labor induction at term. One hundred women were randomized to receive 50 µg of misoprostol either orally or sublingually every 4 hours to maximum of 5 doses. The study revealed that there were no significant differences in the mode of delivery, interventions for fetal distress or

neonatal outcome in two groups. The study concluded better efficacy of sublingual misoprostol as compared to oral misoprostol and more acceptable to the patients<sup>[33]</sup>.

In the recent studies 25 µg has been recommended for efficient and safe method of induction. Previous studies indicated that Misoprostol as effective cervical ripening agent. Now challenge is to administer Misoprostol accurately while

maintaining the ability to discontinue the medication when required. Recent coworkers utilized Misoprostol delivery system that controls Misoprostol release and rapid removal when required, i.e., Misoprostol Vaginal Insert (MVI) delivery system. It is made from a non-biodegradable hydrogel polymer with active ingredient Misoprostol dispersed throughout this polymer matrix. Castaneda *et al.* 2005 conducted a study to identify the maximum tolerable dose and to determine the efficacy of different misoprostol dose reservoir in an intravaginal controlled release hydrogel polymer. Nulliparous women at  $\geq 37$  weeks of gestation requiring cervical ripening and IOL were treated with misoprostol in a controlled release, retrievable hydrogel polymer vaginal insert. Sequential cohorts of 6 patients were to be treated with escalating dose reservoirs of 25, 50, 100, 200 and 300  $\mu\text{g}$ . The insert was to be removed upon onset of active labor at 24 hours or earlier, if treatment related adverse events occurred. The safety end point was determination of the Maximum Tolerable Dose (MTD) based on occurrence of hyperstimulation syndrome and primary efficacy end point was time to vaginal delivery. The study showed that increasing reservoir doses of misoprostol up to 100  $\mu\text{g}$  produced more rapid increases in modified Bishop Scores, less need for oxytocin, and a shorter time to vaginal delivery. Doses above 100  $\mu\text{g}$  did not further enhanced cervical ripening or shortened the time to vaginal delivery. The median to vaginal delivery was 14.2 hours using 100  $\mu\text{g}$  dose. Uterine hyperstimulation and adverse fetal heart rate occurred with 200 and 300  $\mu\text{g}$  inserts. It was concluded that 100  $\mu\text{g}$  vaginal insert resulted in successful cervical ripening and rapid vaginal delivery with an acceptable safety profile for future randomized clinical trials<sup>[34]</sup>. Stephenson *et al.* in 2013 assessed the cardiotocographic abnormalities associated with different misoprostol dosing reservoirs and concluded that the rate of uterine tachysystole was higher in 200  $\mu\text{g}$  MVI group than in the 100  $\mu\text{g}$  MVI group (P,0.001, relative risk 2.11, 95% CI 1.39–3.22). This effect was not noticed between the 150  $\mu\text{g}$  and 100  $\mu\text{g}$

dose reservoirs. However, uterine hyperstimulation syndrome, with fetal heart rate abnormality, was not significantly different between the groups. Most importantly, in patients who had a cesarean delivery, the mean time from onset of tachysystole to delivery was 8.3, 17.7, and 15.5 hours for 100, 150, and 200  $\mu\text{g}$  dose reservoirs, respectively, indicating that very few of these deliveries, if any, were performed for emergent fetal indications related to fetal heart rate abnormality<sup>[35]</sup>.

Wing *et al.*, 2013 compared 1,358 women randomized to receive 200  $\mu\text{g}$  MVI. Time to vaginal delivery and rate of cesarean delivery were the coprimary endpoints. When compared with women treated with the DVI, women treated with the 200  $\mu\text{g}$  MVI had significantly reduced times to vaginal delivery and active labor<sup>[36]</sup>.

Small, frequent, titrated oral doses of misoprostol were successful in avoiding the significant increase in uterine hyperstimulation reported in previous studies, at the expense of a somewhat slower response in achieving vaginal birth in 24 hrs. Souza *et al.* (2013) determined the safety and efficacy of titrated oral misoprostol solution and compared with vaginal misoprostol tablets for labour induction. 200 women with single gestation were randomised to receive a titrated oral solution (initial misoprostol dose 20mg/per hour; dose increased by 20mg/hr every 6hours up to 80 mg/hr for a maximum of 48 doses) or vaginal misoprostol tablets (25mg of misoprostol every 6 hours for a maximum of 8 doses). The study concluded that the frequencies of vaginal delivery could not be achieved within 12 hours (RR 0.87; 95% CI 0.62-1.22) and within 24 hours (RR1.11; 95%CI, 0.83-1.49) were similar in 2 groups. No difference was found in terms of uterine hyperstimulation, unfavourable cervix at 12 and 24 hours, oxytocin augmentation, tachysystole, epidural analgesia, adverse effects and perinatal outcome. The study concluded that titrated oral misoprostol solution was as effective and safe for labor induction as vaginal misoprostol tablets<sup>[37]</sup>.

Deshmukh *et al.* (2017) determined the effect of oral misoprostol solution for IOL in 200 patients undergoing IOL after 36 weeks of pregnancy, who



were allocated by randomisation to IOL with oral misoprostol solution administered 2 hours apart. There was no significant difference in substantive outcomes. Vaginal delivery within 24 hours was achieved in 80.5% of patients. The caesarean section rate was 19.5%. Uterine hyperactivity occurred in 4% of patients. The study concluded that new approach to oral misoprostol solution administration was successful in achieving vaginal delivery rate in 24 hours in 80.5% of patients; rate of CS was less 19.5% [38].

Misoprostol for IOL is not recommended in a scarred uterus. Plaut *et al* 1999 reported their experience with uterine rupture in patients undergoing a trial of labor after previous caesarian delivery in which labor was induced with misoprostol. This report was based on case studies, a computerized search of medical records and literature review. Uterine rupture occurred in 5 of 89 patients with previous caesarian delivery who had labor induced with misoprostol. The uterine rupture rate for patients attempting Vaginal Birth after Cesarean Section (VBAC) was significantly higher in those who received misoprostol, 5.6% more than in those who did not, 0.2% (1 upon 423,  $p=0.0001$ ). IOL is a critical life-saving intervention that reduces adverse outcomes [39].

The possibility of uterine rupture as a rare complication of IOL must be considered. Cases of uterine rupture associated with use of misoprostol for IOL were reported by Majoko *et al.* in 2002. There is a risk of uterine rupture that may be dose dependent. But a case of uterine rupture has been reported in a nulliparous women following a single vaginal dose of 100  $\mu\text{g}$  [40].

### Conclusion

While going through above studies, it can be concluded that different routes of misoprostol administration for IOL needs carefully balancing benefit (shorter induction to delivery interval) against the risk (abnormal uterine contractions and adverse neonatal and maternal outcomes). Further trials comparing the current misoprostol regimen to other regimens will be required to confirm the

proper safety and effectiveness without increasing misoprostol-induced argumentative outcomes. However, the studies to date have been far too small to address the issue of safety. Whatever misoprostol regimens are to be tested in future should be assessed in sufficiently large IOL trials to address the issues of safety as well as effectiveness in an unbiased fashion.

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