

## A prospective study of sublingual misoprostol (PGE1) versus intracervical dinoprostone (PGE2) followed by sublingual misoprostol (PGE1) for induction of labour in singleton full term pregnancy

Rakhee R. Sahu<sup>1,\*</sup>, Anjali Sonawane<sup>2</sup>

<sup>1</sup>Consultant Obstetrician & Gynecologist, <sup>2</sup>Senior Resident, Dr. L. H Hiranandani Hospital, Mumbai

**\*Corresponding Author:**

Email: rakhee.sahu@hiranandanihospital.org

### Abstract

Prostaglandins E1 and E2 have been extensively used for cervical ripening and induction of labour. The objective of our study is to compare the efficacy of sublingual route of misoprostol along with intracervical Dinoprostone gel as induction method.

**Methods:** This is a randomized prospective interventional study conducted in 100 full term pregnant women. Group 1- 50 cases- Tablet Misoprostol 50 mcg sublingual followed by tablet Misoprostol 25 mcg sublingually 4 hourly, to maximum of 200 mcg.

Group 2 – 50 cases - PGE2 gel (0.5mg, 6 hourly two gels) intracervical application followed by tablet Misoprostol 50 mcg sublingual followed by Tab. Misoprostol 25mcg sublingually 4 hourly, to maximum of 200 mcg.

**Results:** There was no significant difference between group 1 and 2 for demographic characteristics, gravidarum, Bishop's score. The mean duration of latent phase for Group 1 was significantly shorter (11hrs 40 min) than that in Group 2 (21hrs 36 min). There was no significant difference in mean duration of active phase of labour between the 2 groups.

In our study the mean induction to delivery interval (IDI) for Group 1 was 15 hrs 16 min (6.33), whereas the mean induction to delivery interval for Group 2 was 25 hrs 3 min (7.43) which was statistically significant (P value <0.0001).

There was no significant difference in mode of delivery and fetal Apgar score between the 2 groups.

**Conclusion:** Misoprostol alone was more efficient than Dinoprostone followed by Misoprostol in terms of short Induction to Delivery interval.

**Keywords:** Induction of labour, Misoprostol, Dinoprostone

### Introduction

Induction of labour is defined as the process of artificially stimulating the uterus to start labour.<sup>(1)</sup> The goal of obstetrics is a pregnancy that culminates in a healthy infant and a minimally traumatized mother. Induction of labour is extensively used all over the world in cases where continuation of pregnancy is hazardous to the mother and/or her fetus.

The use of PGs for cervical ripening has been reported extensively, involving a variety of PG classes, doses, and routes of administration.<sup>(2,3)</sup> Prostaglandins have the dual capability to ripen the cervix and initiate uterine contractility. Currently Misoprostol (synthetic analogue of PGE1) has been approved for the treatment and prevention of peptic ulcer disease related to chronic non-steroidal anti-inflammatory drugs.

The local (intracervical) application of PGE 2 results in direct softening of the cervix by at least three mechanisms:

1. It softens the cervix by altering the extracellular ground substance of the cervix,
2. It increases the activity of the smooth muscle of the cervix and uterus, and
3. It leads to gap junction formation that is necessary for the coordinated uterine contractions of labour.<sup>(4)</sup>

PGE 1 (Misoprostol) stimulates both the tone and amplitude of uterine contractions by increasing the calcium influx and modulation of C-AMP.

The normal human cervix is composed mainly of collagen and 10-15% smooth muscle. The human cervix consists mainly of extracellular connective tissue with the predominant molecules of the extracellular matrix being type 1 and type 3 collagen. Intercalated among the collagen molecules are glycosaminoglycans and proteoglycans, hyaluronic acid, dermatan sulphate and heparin sulphate. Fibronectin and elastin also run among the collagen fibers and it is the release of fibronectin from the interface between the chorion and the decidua that is utilized in tests used to predict preterm labour. It is necessary for the cervix to undergo several changes in order to stimulate the onset of labour and allow dilatation to occur. This process is known as cervical ripening and is the result of a series of complex biochemical reactions resulting in the cervix becoming soft and pliable. Late in pregnancy, hyaluronic acid, cervical collagenase and elastase increase in the cervix. This results in an increase of water molecules which intercalate among the collagen fibers. The amount of dermatan sulphate and chondroitin sulphate decreases, leading to reduced bridging among the collagen fibers. These changes, combined with decreased collagen fiber alignment, decreased collagen fiber strength, and diminished tensile strength of the extracellular cervical matrix, result in the ripening process. An increase in the enzyme cyclooxygenase-2, leads to increased local production of prostaglandin E2 (PGE2) in the cervix. The increase in PGE2 results in numerous changes to the cervix, including dilatation of small vessels in the cervix, an increase in interleukin (IL)

8 release and an increase in collagen degradation mediated by increased chemotaxis for leukocytes. Cervical ripening also involves prostaglandin F<sub>2</sub>-alpha which stimulates an increase in glycosaminoglycans. There is also increased activity of matrix metalloproteinases 2 and 9, enzymes that degrade extracellular matrix proteins.

### Aims and Objectives

**Primary Objectives:** To determine the efficacy and safety profile of sublingual Misoprostol alone versus intracervical Dinoprostone followed by sublingual Misoprostol for cervical ripening and induction of labour.

**Secondary Objectives:** To compare Induction to delivery interval (IDI).

To compare the operative intervention (vacuum, forceps, LSCS) rate between two groups.

### Materials and Methods

**Study Area:** This study was carried out on in-women of Obstetrics and Gynaecology, Department of Dr. L. H. Hiranandani hospital Powai, after obtaining clearance from the hospital ethical and scientific committee.

**Type of Study:** This was a hospital based randomized prospective interventional study.

**Study Population:** The subjects were selected those getting admitted at, Dr. L. H. Hiranandani Hospital for safe confinement in the year 2014-2015.

### Methodology

#### Inclusion Criteria:

- Singleton Pregnancy
- Live fetus
- Cephalic presentation
- Bishop's Score  $\leq$  6
- Completed 37 weeks of pregnancy
- No detectable uterine contractions

#### Exclusion Criteria:

- Ante partum Hemorrhage
- Para  $\geq$  4
- Previous uterine scar / any other uterine surgery
- Severe oligohydramnios (AFI <3cms)
- Polyhydramnios (AFI >25cms)
- Non-reassuring fetal heart rate pattern
- IUGR
- Cephalo-pelvic disproportion
- Renal and Hepatic diseases
- Hypersensitivity to Prostaglandins
- Chorioamnionitis (Hyperthermia >38<sup>0</sup>c)

All women fulfilling the inclusion criteria were included in this study. After taking written and informed consent and doing detailed history and examination NST was performed to evaluate the fetal well-being.

Then women were randomized into two groups with

the help of computer generated system.

**Group 1** - 50 cases- Tablet Misoprostol 50 mcg sublingual followed by tablet Misoprostol 25 mcg sublingually 4 hourly, to maximum of 200 mcg.

**Group 2** – 50 cases- PGE<sub>2</sub> gel (0.5mg, 6 hourly two gels) intracervical application followed by tablet Misoprostol 50 mcg sublingual followed by Tab. Misoprostol 25mcg sublingually 4 hourly, to maximum of 200 mcg.

There was protocol (data collection form) designed for cervical ripening and induction of labour for each Group where record was kept.

- Women's vitals like pulse, Blood pressure, Respiratory System and Cardiovascular system were monitored 1 hourly during labour
- Frequency and duration of uterine contractions were monitored 1 hourly in latent phase, every 30 minutes in active phase and every 15 minutes in second stage of labour.
- Continuous electronic fetal heart rate monitoring was performed in all women during active phase of labour.
- Any adverse drug effects on mother (uterine tachysystole, any gastrointestinal abnormality, fever) and fetus (fetal heart rate abnormality, passage of meconium) were noted.
- After Dinoprostone gel instillation women were made to lie down for at least 30 minutes.
- Tab Misoprostol was discontinued after 3-4 cm of cervical dilatation and/or adequate uterine contractions i.e. 3 contraction every 10 minutes lasting for 30- 40 seconds were achieved.
- All women were monitored for progress of labour. If there was arrest of cervical dilatation or arrest of descent of fetal head and if uterine contractions were inadequate, IV infusion of oxytocin with titrating dose was advised for all the women.
- After artificial rupture of membranes (ARM) was done at 4-5 cm of cervical dilatation, the colour of amniotic fluid was noted.
- Labour induction was considered successful if subjects delivered within 24 hours of initiation of either of two methods. Participants were observed for first four hours postpartum and any maternal side effects were recorded in detail.
- Record of Latent Phase and active phase of labour was kept.
- Record of mode and route of delivery, indications for cesarean delivery, number of emergency cesareans performed for abnormal FHR pattern, for meconium stained liquor, for non-progress of labour was kept.
- Number of doses of Dinoprostone gels and Misoprostol Tablets used, oxytocin augmentation and incidence of any adverse effects was noted.
- Specific prostaglandin side effects such as

hyperpyrexia, vomiting and diarrhea, incidence of postpartum hemorrhage, cervical tears, and vaginal tears were recorded.

- Fetal monitoring in terms of birth weight, Apgar score at 5 minute, admission to neonatal intensive care unit was done.

#### Data Analysis:

- We calculated the mean and standard deviation for continuous variables.
- We calculated the proportion for categorical variables.
- The means were compared using the t- test.
- Since these were two different groups, we used the unpaired t- test.
- The proportions were compared using the Chi square test or Fishers Exact test for low expected cell count.
- A p value of <0.05 was considered to be statistically significant.
- Data were analyzed using STATA Version 13.

#### Discussion

Cervical ripening methods fall into two main categories i.e. Pharmacologic and mechanical methods.

#### Pharmacologic Methods

- Oxytocin
- Prostaglandins -- E2 (Dinoprostone, Prepidil gel and Cervidil time-released vaginal insert)
- E1 (Misoprostol, Cytotec)
- Estrogen
- Relaxin
- Hyaluronic acid
- Progesterone receptor antagonists (RU 486)

The various mechanical methods for cervical ripening are Amniotic membrane stripping, Amniotomy and Mechanical dilators like Laminaria tents, Dilapan, Lamical, Transcervical balloon catheters with extra-amniotic saline infusion or with concomitant oxytocin

administration.

In 2011, WHO issued guidelines on induction of labour, which included the use of oral and vaginal Misoprostol for induction of labour. These guidelines are based partly on the findings of the three Cochrane reviews evaluated in this commentary. Adaptation and implementation of these guidelines in different settings is endorsed.<sup>(16)</sup>

ACOG recommends in its ACOG Practice bulletin August 2009, the use of low dose Misoprostol approximately 25 mcg of Misoprostol should be considered as the initial dose for cervical ripening and labour induction. The frequency of administration should not be more than every 3 to 6 hours.<sup>(19)</sup>

In 1992, the U.S. Food and Drug Administration (FDA) approved PGE2 (0.5 mg intracervical) for cervical ripening and labour induction.<sup>(5)</sup> (WHO Recommendations for induction of labour 2011).<sup>(16)</sup>

In Our study we have compared the efficacy and safety profile of sublingual Misoprostol alone versus intracervical Dinoprostone followed by sublingual Misoprostol for cervical ripening and labour induction.

There was no significant difference between the Groups in terms of their Demographic characteristics (Age, Height, Weight, BMI, gravid, Bishop Score).

**Table 1: Distribution of cases, according to the parity of the Women**

Group	Obstetric History			p-value
	Primi-Para	Multi-Para	Total	
Group 1	47 (94%)	3(6%)	50 (100)	0.295
Group 2	44(88%)	6 (12%)	50 (100)	
Total	91(91%)	9 (9%)	100 (100%)	

There was no significant difference in the proportion of Primi-para and Multi-para across the two groups (p value 0.295).

**Table 2: Indication for induction of labour**

Group	Indication of induction								p-value
	1 (Elective) (%)	2 (PIH) (%)	3 (Diabetes) (%)	4 (Other) (%)	5 (Loop of cord) (%)	6 (Post datism) (%)	7 (Multiple indications) (%)	Total (%)	
Group 1	24 (48)	2 (4)	3 (6)	3 (6)	9 (18)	6 (12)	3 (6)	50 (100)	0.238
Group 2	23 (46)	1 (2)	3 (6)	12 (24)	7 (14)	3 (6)	1 (2)	50 (100)	
Total	47 (47)	3 (3)	6 (6)	15 (15)	16 (16)	9 (9)	4 (4)	100 (100)	

4) Other (Oligohydramnios, Cholestasis of pregnancy, Hypothyroidism)

There was no significant difference in the indication for induction across the two groups.

(p value 0.238)

**Table 3: Mean bishop score**

Group	Mean Bishop score	Std Dev	p value
Group 1	2.36	0.98	0.9266
Group 2	2.34	1.17	

There was no significant difference in the mean Bishop score across the groups.

With p value being (0.9266)

All 100 cases had Bishop score of less than 6.

In our study it was observed that though lesser dose of Misoprostol (PGE1) was required when it was used following Dinoprostone (PGE2) it did not significantly reduce the total dose requirement of Misoprostol for induction of labour.

**Table 4: Total dose of Misoprostol required**

Group	Mean	Std Dev	p value
Group 1	102.50	42.33	0.40
Group 2	94.50	52.32	

The Mean (S.D.) dose of Misoprostol required for induction of labour for Group 1 was 102.50 (42.33).

The Mean (S.D.) dose of Misoprostol required for induction of labour for Group 2 was 94.50 (52.32). It was seen that lesser dose of Misoprostol was required in Group 2.

There was no significant different in the mean total dose of Misoprostol required for induction of labour across the Groups (p value 0.4026)

The mean duration (S.D.) of latent phase for Group 1 was 11hrs 40 min (6.55), whereas the mean duration (S.D.) of latent phase for Group 2 was 21hrs 36 min (7.89). Misoprostol (PGE1) only Group had shorter latent phase or time taken for onset of labour was less in Misoprostol only Group compared to Dinoprostone followed by Misoprostol Group. This was comparable to the study done by Patil P, Patil A in 2013, on Misoprostol v/s Cerviprime Gel for Induction of Labour,<sup>(21)</sup> where the mean time taken for onset of labour was less in Misoprostol Group (43.22 min v/s 1 hr 40 min).

**Table 5: Duration of latent phase of labour**

Group	Mean	Std Dev	p value
Group 1	11hrs 40 mins	6.55	<0.0001
Group 2	21hrs 36 mins	7.89	

There was significant difference in the mean duration of latent phase between the two groups.

The mean duration (S.D.) of latent phase for group 1 was 11 hrs 40 min (6.55).

The mean duration (S.D.) of latent phase for group 2 was 21 hrs 36 min (7.89).

**Table 6: Duration of active phase of labour**

Group	Mean	Std Dev	p value
Group 1	4.71	1.83	0.4915
Group 2	4.44	1.44	

There was no significant difference noted in mean duration of active phase of labour across the two Groups. (p value 0.4915) Mean time (S.D.) required for Active phase of labour was 4.71(1.83) hrs for Group 1 whereas 4.44(1.44) hrs for Group 2.

In our study there was no significant difference in terms of need of augmentation of labour with Pitocin (Oxytocin) across both the Groups (p value of 0.687), 58% of women from Group 1 whereas 54% of women from Group 2 required augmentation of labour with Pitocin. Similar Observation was made by Girija Shivarudraiah et al (April 2011)<sup>(23)</sup> in their study.

In present study we found that there was significant difference in induction to delivery interval between two Groups. The induction delivery interval (IDI) is the gold standard for judging the efficacy of any inducing agent. In our study, mean IDI was shorter with Misoprostol induction as compared to Dinoprostone followed by Misoprostol induction. In our study the mean (S.D.) induction to delivery interval for Group 1 was 15 hrs 16 min (6.33), whereas the mean (S.D.) induction to delivery interval for Group 2 was 25 hrs 3 min (7.43) (P value <0.0001). This was comparable to results from other studies. In study by Patil P, Patil A<sup>(21)</sup> in 2013, the mean induction to delivery interval was less in the misoprost Group (5 hrs 02 min v/s 11 hrs 12 min), which is statistically significant (P = <.001). Similar results were seen in study done in 2003 by Agarwal et al,<sup>(21)</sup> where it was 12.8+/- 6.4 hrs v/s 18.53+/-8.5 hours. Also in another study of Murthy Bhaskar Krishnamurthy,<sup>(21)</sup> which was done in 2006, induction delivery interval was shorter in the Misoprostol Group. Similar observations were made in study done by Amandeep K. Anand, Shahida Mir<sup>(22)</sup> in 2012. The mean induction delivery interval (IDI) was 651.47 minutes (11.26 hours) in Group 'A' i.e. Misoprostol Group and 798.62 minutes (13.31 hours) in Group 'B' i.e. Dinoprostone Group and was highly significant (p<0.01).

**Table 7: Total induction to delivery interval (IDI)**

Group	Mean	Std Dev	p value
Group 1	15 hrs 16 mins	6.33	<0.0001
Group 2	25 hrs 3 mins	7.43	

There was significant difference in mean induction to delivery interval between two groups. (p value <0.0001)

The Mean (S.D.) induction to delivery interval for group 1 was 15 hrs 16 mins (6.33) whereas, the Mean (S.D.) induction to delivery interval for group 2 was 25 hrs 3 min (7.43).

Induction to delivery interval was much lesser in Group 1 compare to Group 2.

In our study there was no significant difference in the mode of delivery across the two Groups (P value 0.694).

**Table 8: Mode of Delivery**

Group	FTND/ Vacuum/ Forceps/LSCS					p value
	FTND	Vacuum	Forceps	LSCS	Total	
Group 1	21 (42)	13 (26)	1 (2)	15 (30)	50 (100)	0.694
Group 2	17 (34)	15 (30)	0(0)	18 (36)	50 (100)	
Total	38 (38)	28 (28)	1(1)	33 (33)	100 (100)	

There was no significant difference in the mode of delivery across the two groups (p value 0.694).

The incidence of vaginal delivery in Group 1 was 70% and in Group 2 was 64%, which is not statistically significant. In a study done in 2013 by Patil P, Patil A<sup>(21)</sup> Misoprostol was able to increase the vaginal deliveries compared to the control group as 94% women delivered vaginally in study group (Misoprostol), Compared to 78% in the control (Dinoprostone) group.

In our current study vacuum assisted deliveries were seen in 26% of cases from Group 1 and 30% of cases from Group 2.

In our study 30% of cases from Group 1 whereas 36% of cases from Group 2 underwent caesarean section. Implying though caesarean section rate was higher in Group 2 it was not statistically significant.

**Table 9: Indications of caesarean section**

Type	Indications for LSCS				p value
	1 (Fetal Bradycardia)	2 (NPOL)	3 (MSAF)	Total	
Group 1	6 (40)	5 (33.33)	4 (26.67)	15 (100)	0.004
Group 2	1 (5.56)	16 (88.89)	1 (5.56)	18 (100)	
Total	6 (21.21)	17 (63.64)	3 (15.15)	33 (100)	

2) NPOL: Non progress of labour

3) MSAF: Meconium stained amniotic fluid

There was significant difference in the indication of LSCS across two Groups (p value 0.004)

With Fetal Bradycardia and MSAF being most common indication in Group 1 & Non progress of labour the most common indication of LSCS of Group 2.

There was no significant different in the 5minutes APGAR score across the two Groups.

No baby required NICU admission.

This was comparable to the study by Amandeep K. Anand, Shahida Mir (2012)<sup>(22)</sup> where Caesarean section rate was 15% with Misoprostol induction and 24% with Dinoprostone induction Group.

In present study 42% of cases from Group 1 whereas 34% of cases from Group 2 had Full Term Normal Delivery, in study by Amandeep K. Anand, Shahida Mir (2012)<sup>(22)</sup> Normal spontaneous vaginal delivery occurred in 75 (75%) participants in Misoprostol Group and 70 (70%) participants in Dinoprostone Group. In our study only 2% of cases from Group 1 had Forceps assisted delivery.

In our study we found that there was significant difference in the indication of LSCS between the two Groups (P value 0.004), 40% of cases of Group 1 underwent LSCS for Fetal bradycardia whereas only 5.56% of cases of Group 2 underwent LSCS for Fetal bradycardia.

Indicating Fetal Bradycardia was the most common indication for Caesarean Section in Group 1.

In current study Non Progress of Labour was the most common indication for caesarean section in Group 2, as 33.33% of cases of Group 1 underwent LSCS for Non Progress of Labour whereas 88.89% of Group 2

cases underwent LSCS for Non Progress of Labour.

Meconium Stained amniotic fluid was the 2<sup>nd</sup> most common indication of caesarean section in Group 1, as 26.67% of cases of Group 1 whereas 5.56% of Cases of Group 2 underwent caesarean section for meconium stained amniotic fluid. This was comparable to the results obtained by Amandeep K. Anand, Shahida Mir (2012).<sup>(22)</sup>

There was no significant difference in the Mean Birth weight of the babies across the two Groups (P value 0.4467). The Mean birth weight (S.D) of Group 1 babies was 3.04 kg(0.47) whereas the Mean birth weight (S.D.) of Group 2 babies was 3.10kg (0.35).

In our study there was no significant difference in the 5 minute Apgar score of babies across the two Groups. All babies had 5 minute Apgar score of 9/10. Similar Apgar scores were noted in Misoprostol versus Dinoprostone Groups in studies done by Aihai Liu, Jieqiang Lv1 (2014)<sup>(20)</sup>, In our study significant difference was seen in the type of complications which were observed across the two groups (p value 0.041).

In current study 6% of babies from Group 1 whereas 4% of babies from Group 2 had bradycardia. Meconium stained amniotic fluid was seen 12% of women from

Group 1 and in 2% of cases from Group 2 though it was associated in combination with other complication. One case from Group 1 had hyperpyrexia which was managed symptomatically.

No evidence of Gastro-intestinal side effects such as nausea, vomiting were noted. No incidence of uterine tachysystole, post-partum hemorrhage was seen.

In our study there was significant difference in the total number of cases opting for Epidural Analgesia (P value 0.016).

Epidural Analgesia was opted by 60% of women from Group 1, whereas 36% of women of Group 2 opted for epidural analgesia.

There was no significant difference in the incidence of any complications in Post-dated pregnancies compared to term pregnancies. (P value 0.620)

There was no significant difference in the incidence of LSCS in Post-term pregnancies compared to the term pregnancies. (P value >0.99)

### Conclusion

This study was conducted in 100 women of comparable age, gestational age, parity and Bishop Score, out of which 50 participants were induced with sublingual Misoprostol tablets (Group1) and 50 participants were induced with intracervical Dinoprostone gel followed by sublingual Misoprostol (Group 2). In present study, we found that the duration of latent phase was significantly shorter in Group 1 than Group 2, with almost comparable duration of Active phase of labour, indicating that Misoprostol alone is more effective than Dinoprostone followed by Misoprostol for cervical ripening and inducing labour.

The induction delivery interval (IDI) is the gold standard for judging the efficacy of any inducing agent. In our study the mean (S.D.) induction to delivery interval for Group 1 was 15 hrs 16 min (6.33), whereas the mean (S.D.) induction to delivery interval for Group 2 was 25 hrs 03 min (7.43) (P value <0.0001). In our study, mean IDI was significantly shorter with Group 1 as compared to Group 2. Thus came to conclusion that Misoprostol alone was more efficient than Dinoprostone followed by Misoprostol in terms of short Induction to Delivery interval. Fetal Bradycardia (Distress) was seen more with the Group 1 than Group 2 making it as the most common indication of LSCS of Group1. This could be the due to more frequency and intensity of uterine contractions as compared to group 2.

Non-Progress of labour was most commonly seen with group 2. This was mainly due to prolonged Latent phase of labour. Though no significant difference was noted in terms of the Caesarean section rate between the two groups. The neonatal outcomes were comparable in our study across the two groups.

### Recommendations

Our study concluded that sublingual Misoprostol was more efficient than intracervical Dinoprostone

followed by sublingual Misoprostol in reducing induction to delivery interval to less than 24 hrs and had no significant maternal or fetal complications. So we recommend the use of Low dose sublingual Misoprostol for induction of labour.

Injudicious use of Misoprostol may lead to uterine tachysystole (hyper-stimulation), uterine rupture and fetal complications hence close maternal and fetal monitoring is recommended.

We further would like to recommend studying the role, use and safety of different combinations of prostaglandins in a larger population.

### References

1. Managing complication in pregnancy and childbirth: a guide for midwives and doctors. Geneva, World Health Organization, 2000 (available at: [http://www.who.int/reproductivehealth/publications/maternal\\_perinatal\\_health/9241545879/en/index.html](http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9241545879/en/index.html)).
2. Deborah A. Wing and Christine K. Farinelli Abnormal Labour and Induction of Labour Steven G. Gabbe MD Obstetrics: Normal and Problem Pregnancies, 6edition 2012;287-310Saunders Title ISBN: 978-1-4377-1935-2.
3. Induction of Labour and Termination of the Pre-viable Pregnancy Luis Sanchez-Ramos and ISAAC DELKE High-Risk Pregnancy, Fourth Edition, chapter 66,1145-1168.e2©2011.
4. Stempel JE, Prins RP, Dean S, et al: Pre-induction cervical ripening: A randomized prospective comparison of the efficacy and safety of intravaginal and intracervical prostaglandin E 2 gel. Am J Obstet Gynecol 1997; 176: 1305-1309.
5. World Health Organization, Maternal and Newborn Health/Safe Motherhood Unit. Care in normal birth: a practical guide. [http://www.who.int/maternal\\_child\\_adolescent/documents/who\\_frh\\_msm\\_9624/en/](http://www.who.int/maternal_child_adolescent/documents/who_frh_msm_9624/en/).
6. ACOG. American College of Obstetricians and Gynecologists Practice Bulletin. Dystocia and augmentation of labour. Clinical management guidelines for obstetricians-gynecologists. No 49. American College of Obstetricians and Gynecologists: Washington, DC; December 2003.
7. Norwitz ER, Robinson JN, Repke JT. Labour and delivery. Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and problem pregnancies. 3rd ed. New York: Churchill Livingstone;2003.
8. Induction of labour Fergus P McCarthy Louise C Kenny: Obstetrics, Gynaecology and Reproductive Medicine 24:1;2013 Published by Elsevier Ltd.
9. Laws PJ, Sullivan EA. Australia's Mothers and Babies 2002. AIHW Cat. No. PER 28. Sydney: AIHW National Perinatal Statistics Unit (Perinatal Statistics Series No. 15), 2004.
10. National Collaborating Centre for Women's and Children's Health. Induction of Labour. London, UK: RCOG Press; 2008.
11. WHO Global Survey on Maternal and Perinatal Health. Induction of labour data. Geneva; World health Organization: 2010.
12. SJ Stock • AA Calder Induction of Labour Baskett, Thomas F. Munro Kerr's Operative Obstetrics, Twelfth Edition 2014;71.
13. ACOG Practice Bulletin Clinical management guidelines for obstetrician and gynaecologist; number 107: August 2009.

14. Eroglu D, Oktem M, Yanik F, Kuscü E. Labour induction at term: a comparison of the effects of 50 microg and 25 microg vaginal Misoprostol. *Clin Exp Obstet Gynecol* 2007;34:102–5.
15. Drug Monograph Misoprostol Gold Standard. Published December 8, 2011.
16. WHO recommendations for induction of labour. Geneva: World Health Organization, 2011(available at: [http://whqlibdoc.who.int/publications/2011/9789241501156\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501156_eng.pdf)).
17. Cervidil (Dinoprostone) vaginal insert package insert. East Kilbride, Scotland: Ferring Controlled Therapeutics Limited; 2012 Oct.
18. Prepidil Gel (Dinoprostone) cervical gel package insert. New York, NY: Pfizer Inc.; 2010 Feb.
19. ACOG Practice Bulletin Clinical management guidelines for obstetrician and gynaecologist; number 107: August 2009.
20. Efficacy and safety of intravaginal Misoprostol versus intracervical Dinoprostone for labour induction at term: a systematic review and meta-analysis. Liu A, Lv J, Hu Y, Lang J, Ma L, Chen W - *J. Obstet. Gynaecol. Journal of Obstetrics and Gynaecology Research (Impact Factor: 0.93)*. 04/2014;40(4). DOI: 10.1111/jog.12333.
21. Patil P1, Patil A2. Misoprostol v/s Cerviprime Gel for Induction of Labour. *Int J Med Res Rev* 2013;1(2):63-70.
22. A randomized comparison between Intravaginal Misoprostol and Intracervical Dinoprostone for Cervical Ripening and labour induction in Participants with Unfavourable Cervices; Amandeep K. Anand, Shahida Mir: Deptt. of Obst and Gyane, Govt Medical College Srinagar, Kashmir- J&K India, *jkscience* Vol. 14 No. 3, July - September 2012.
23. A Randomized Controlled Trial Comparing Low Dose Vaginal Misoprostol and Dinoprostone Gel for Labour Induction Girija Shivarudraiah, Manjunath Attibe Palaksha. *The Journal of Obstetrics and Gynecology of India* March/ April 2011 pg 153 – 160.
24. Austin SC, Sanchez-Ramos L, Adair CD. Labour induction with intravaginal Misoprostol compared with the Dinoprostone vaginal insert: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2010;202:624.e1-9.
25. Induction of labour with intravaginal Misoprostol and prostaglandin E2 gel: a comparative study. Nanda S, Singhal SR, Papneja A *Trop Doct.* 2007 Jan;37(1):21-4. PMID:17326881[PubMed - indexed for MEDLINE].
26. Alfievic Z, Aflaifel N, Weeks A. Oral Misoprostol for induction of labour. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD001338. DOI:10.1002/14651858.CD001338.pub3.
27. Balancing the efficacy and safety of Misoprostol: a meta-analysis comparing 25 versus 50 micrograms of intravaginal Misoprostol for the induction of labour K McMaster\*, L Sanchez-Ramos and AM Kaunitz Article first published online: 3 JUL 2014 DOI: 10.1111/1471-0528.12935 © 2014 Royal College of Obstetricians and Gynaecologists.
28. World Health Organization, Maternal and Newborn Health/Safe Motherhood Unit. Care in normal birth: a practical guide. [http://www.who.int/maternal\\_child\\_adolescent/document/s/who\\_frh\\_msm\\_9624/en/](http://www.who.int/maternal_child_adolescent/document/s/who_frh_msm_9624/en/).