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Low dose vaginal misoprostol in the management of women with intrauterine fetal death

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Abstract
Background and Objectives: A prospective observational cohort study was conducted to evaluate the effectiveness and side effects of vaginal misoprostol in the termination of second and third trimester pregnancies complicated with intrauterine fetal death.
Material and Methods: The present study was conducted at the Department of Obstetrics and Gynaecology, Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram (Dist.), Andhra Pradesh state, India. The study subjects constituted n = 100 women subjects with intrauterine fetal demise in second and third trimester pregnancies collected from the hospital attached to the Maharajah's Institute of Medical Sciences. All the study group participants were subjected to history taking, physical examination, Bishop scoring, application of 25µg of misoprostol in the posterior fornix of vagina every fourth hourly over 24 hours. The progress, adverse effects and outcomes were assessed.
Results: The success rate was 92.76% and 64.52% in the subjects with third and second trimesters respectively. The mean induction-delivery interval was 15.67 ± 9.64 and 24.94 ± 8.23 for women participants with third and second trimesters respectively. The induction-delivery interval correlated negatively with the duration of gestation. The mean value of total required dose of misoprostol was 192.42 ± 128.99 and 361.29 ± 139.92 for the subjects with third and second trimesters respectively.
Conclusion: Low dose Misoprostol appears to be a safe, effective, practical and inexpensive method for termination of third trimester pregnancies compared to second trimester pregnancies complicated with intrauterine fetal death and its effects increases with duration of gestation.

Keywords: Intrauterine fetal death, induction of labour, Misoprostol

Introduction
The management of intrauterine fetal death (IUFD) poses a dilemma for obstetrician confronted [1]. The frequency of IUFD with a retained fetus varies but is estimated to occur in 1% of all pregnancies [2]. Although a significant number of these patients will spontaneously go into labour with in a several weeks, many do not [1]. The options for health care are either to await onset of spontaneous labour or to induce labour [2]. The medical consequences of postponing delivery can be significant in view of complications like disseminated intravascular coagulopathy (DIC). This increases the risk of severe bleeding complications or haemorrhage [3] and even maternal death. The danger of complications like amniotic embolism is also greater [4].
Induction of labour is a common and evidence based practice in obstetrics. In cases of intrauterine fetal death with a retained fetus, the choice to induce labour in a patient with ripe cervix is straightforward and procedure often uncomplicated. But the complexity in medical management increases significantly when the cervix is unripe or unfavorable (Bishop Score< 6) [2]. Inducing labour in a pregnant woman with an unripe cervix is associated with failed induction of labour and a higher risk of caesarean delivery [2].
Oxytocin which is the most commonly used drug for induction of labour is frequently ineffective in stimulating the uterus especially the pre-term ones. Earlier, high doses of oxytocin infusion were commonly used in this situation. However, the uterine responsiveness to oxytocin varies enormously. Certain other methods of induction of labour like amniotomy and intra-amniotic instillation of prostaglandins are not suitable because of the possible risk of sepsis [3]. These problems have been dramatically reduced with the local or systemic use of prostaglandins. Misoprostol, a synthetic analogue of prostaglandin E_1 [4, 6] is effective and inexpensive, stable at room temperature, easy to administer, and does not require direct supervision during the induction.

It has become an important drug in the practice of obstetrics and gynaecology because of its ability to bring about cervical changes and uterine contractions [6]. A large body of evidence shows that the use of misoprostol for labour induction is highly efficacious and safe.

The vaginal route is advantageous because peak levels are reached slowly and sustained for long and this is associated with fewer side effects as it bypasses the first pass metabolism. Hence vaginal route is more effective than the oral route [1].

The issues related to the proper use of misoprostol are somewhat different for women who have need for labour induction in case of IUFD compared to those with live fetuses. This is because the issues related to fetal wellbeing are eliminated. However, the concerns regarding other side effects such as uterine over activity (hyper stimulation, hypertonus and tachysystole) due to the direct effect on cervix and systemic response (nausea, vomiting, diarrhoea and shivering) remain the same as with live fetuses [2].

In view of the above, this study was undertaken to evaluate the efficacy of low doses of misoprostol in termination of pregnancies with IUFD.

Aim and Objectives

The aim of this work was to evaluate the effectiveness and side effects of repeated vaginal administration of small doses of misoprostol in termination of second and third trimester pregnancies complicated with IUFD.

Materials and Methods

Source of data

The study population consisted of 100 pregnant women subjects with intrauterine fetal death admitted to the hospital attached to the Maharajah's Institute of Medical Sciences, Nellimarla, Vizianagaram (Dist.), Andhra Pradesh state, India.

All the selected subjects participated in the study were subjected to history taking, general, clinical examination, and ultrasound examination. Counseling of the patient was done and written consent was obtained. The induction regimen includes application of misoprostol 25 µg tablet in the posterior fornix of the vagina every 4 hours (up to 6 doses) after determination of Bishop score.

If the first dose does not lead to effective contractions the subsequent dose could be doubled to 50 µg to 100 µg after 4 hours.

- If no efficient regular uterine contractions occurred after 6 doses, augmentation of uterine contractions to be done by oxytocin drip, 4 hours after last misoprostol dose.
- Recording the total dose of misoprostol received and the need for surgical interference to remove the dead fetus or the retained placenta or both.
- The induction trial was considered successful when induction delivery interval was less than 24 hours.
- Failure of delivery within 24 hours is considered "failed trial' but it's not the indication to stop the trial i.e. the trial will be completed till termination.
- Observation of patients for 24 hours after delivery.
- Any complication during induction and 24 hours after delivery were reported.

Inclusion Criteria

- The patient with Intrauterine Fetal Death (IUFD) with gestational age from 13 weeks to term, absent spontaneous labour pain and bishop cervical score < 9.
- The patients with IUFD with gestational age from 13 weeks to term in spontaneous labour pain with Bishop cervical score > 6.
- Group - I: Pregnancies from gestational age 13 weeks to 26 weeks (2nd trimester) complicated with IUFD as documented by USG examination.
- Group - II: Pregnancies beyond 26 weeks of gestational age (3rd trimester) complicated with IUFD as documented by USG examination.

Exclusion Criteria

- Contraindications to misoprostol induction: allergy to prostaglandins.
- Contraindications to vaginal delivery such as: placenta previa, transverse lie, CPD
- IUFD with complications like disseminated intravascular coagulopathy (DIC), amniotic embolism, shock.
- Previous LSCS or any other uterine surgeries like hysterotomy.

In all subjects written consent was taken and cervical status assessed prior to induction.

Modified Bishop score

Score	0	1	2	3
Dilatation of cervix (cms)	<1	1-2	2-4	>4
Length of cervix (cms)	4	2-4	1-2	<1
Position of cervix	Posterior	Mid, Anterior	-	-
Consistency of cervix	Firm	Average	Soft	-
Station of presenting part	-3	-2	-1/0	+1/+2

Prior to each dose modified bishop score was assessed. The dosage was repeated every 4th hourly until an adequate contraction pattern sets in (establishment of 3 uterine contractions in a period of 10 min) or once the cervical dilatation reaches 4 cm, maximum up to 5 doses. After induction, the subjects were monitored for signs of labour, when labour ensued they were closely monitored for maternal vital signs and progress of labour.

Maximum allowable doses were 6. If labour did not ensue even after 4 hours following last dose, induction was stopped and an alternative method of induction used.

The following parameters were noted like number of doses, escalation of doses and in the interval between induction to onset of uterine contraction, induction delivery interval, mode of delivery, maternal complications and adverse effects of medication like fever, diarrhoea, nausea and others.

Tachysystole was defined as more than 5 uterine contractions per 10 min.

Statistical analysis

The qualitative data was expressed as percentage (%) and quantitative statistical analysed data as mean ± Standard Deviation (SD) and *p* value.

Results

The total number of subjects selected for the present study consisted of n = 100, and were divided into two groups: second and third trimester pregnant ladies with intra uterine fetal death (IUFD). There were n = 31 subjects in 2nd trimester (T2) and n = 69 subjects in 3rd trimester (T3).

In this study the data of the distribution of the subjects based on the age presented in Table 1 shows that majority of the cases were in the age group between 21 - 25 years ranging between 18 - 35 years.

Table 1: Distribution of the subjects based on the age.

Age (yrs)	T2	T3
	Number (%)	Number (%)
≤ 20	5 (16.1)	9 (13.0)
21-25	13 (41.9)	33 (47.8)
26-30	11 (35.5)	21 (30.4)
≥ 31	2 (6.5)	6 (8.7)
Total - Number (%)	31 (100.0)	69 (100.0)

The data of distribution of the subjects according to parity shown in the Table 2 shows that there is an equal incidence of primigravida and multigravida, majority of the subjects belonging to 3rd trimester in both primi as well as multigravida.

Table 2: Distribution of the subjects according to parity

Gestational age	Primigravida	Multigravida
	Number (%)	Number (%)
T2	17 (34.0)	14 (28.0)
T3	33 (66.0)	36 (72.0)
Total	50	50

The data of the distribution of the subjects based on associated conditions presented in the Table 3 shows that in this study n= 29 subjects were recorded having hypertensive disorders of pregnancy and n = 10 cases abruptio placenta.

There was n = 1 case of congenital anomaly - open spina bifida.

Table 3: Distribution of the subjects based on associated conditions

Associated conditions	Gestational age	
	T2 - Number (%)	T3 - Number (%)
Antepartum eclampsia	2 (6.50)	5 (7.20)
Severe PE	4 (12.90)	13 (18.80)
Mild PE	0 (0.00)	1 (1.40)
Gestational hypertension	0 (0.00)	3 (4.30)
Chronic hypertension	1 (3.20)	1 (1.40)
Complete HELLP	0 (0.00)	1 (1.40)
Abruptio placenta	0 (0.00)	10 (14.50)
HIV reactive status	0 (0.00)	1 (1.40)
Hypothyroidism	1 (3.20)	0 (0.00)
Oligohydromnios	0 (0.00)	2 (2.90)
PROM	0 (0.00)	1 (1.40)
PPROM	0 (0.00)	1 (1.40)
Severe anaemia	2 (6.50)	2 (2.90)
Rh negative status	2 (6.50)	0 (0.00)
Anomalous baby	1 (3.20)	0 (0.00)
Total - Number (%)	31 (100.0)	69 (100.0)

The data of modified Bishop score before induction represented in the Table 4 shows that in the current study majority of the subjects in T2 group were recorded having score < 6 whereas, in T3 group between 4 and 7. The mean and standard deviation of the score in T2 group is 4.55 ± 1.76 and T3 group is 5.10 ± 1.94

Table 4: Modified Bishop Score before induction.

Score	Gestational age	
	T2 - Number (%)	T3 - Number (%)
0	4 (12.9)	4 (5.8)
2	5 (16.1)	5 (7.2)
3	4 (12.9)	9 (13.0)
4	3 (9.7)	13 (18.8)
5	5 (16.1)	10 (14.5)
6	6 (19.4)	9 (13.0)
7	4 (12.9)	12 (17.4)
8	0 (0.00)	3 (4.3)
9	0 (0.00)	4 (5.8)
Total	31 (100.0)	69 (100.0)
Mean ± SD	4.55 ± 1.76	5.10 ± 1.94

T value = 2.56; *p* value = 0.416 (>0.05) (NS)

The data presented in the Table 5 shows the distribution of cases according to the required number of doses of Misoprostol for induction by vaginal route. Majority of the subjects in T2 group needed 6 doses whereas, majority patients in T3 group needed 1-3 doses, with mean and standard deviation 4.80 ± 1.10 and 3.17 ± 1.65 respectively which is statistically highly significant (with *p* value 0.012).

Table 5: Response of subjects to the dosage of the drug

No. of doses	Gestational age	
	T2 - Number (%)	T3 - Number (%)
1	0 (0)	13(18.8)
2	1 (3.2)	15(21.7)
3	2 (6.5)	13(18.8)
4	10 (32.3)	12(17.4)
5	7 (22.6)	7(10.1)
6	11 (35.5)	9(13.0)
Total	31 (100.0)	69(100.0)
Mean ± SD	4.80 ± 1.10	3.17 ± 1.65

T value = 1.14, *p* value = 0.012 (<0.05) (HS)

The data of the escalation of doses is presented in the Table 6 shows that about 70% of the cases in T2 needed increased dosage up to 100 µgm whereas, in T3 group only a few cases needed increase in dosage which is only up to 50 µgm. The majority of the subjects in T3 group not need any escalation of dosage and delivered with 25 µgm dose alone.

Table 6: Escalation of doses in the subjects

Dosage µgm	T2 – Number (%)	T3 - Number (%)
25	-	47 (68.11)
50	9 (29.03)	22 (31.88)
100	22 (70.96)	-
Total	31	69

In the T2 group, most of the cases had onset of pain between 4 - 40 hrs, after the initial administration of the drug whereas, in T3 group the onset of pain was between 1/2 -28 hrs (Table 7). The mean and standard deviation in T2 is 18.63 ± 8.17 and T3 is 9.22 ± 6.73. The *p* value is 0.024 and is statistically significant.

Table 7: Induction to pain interval (IPI) in relation to gestational age

IPI (hrs)	Gestational age	
	T2 - Number (%)	T3 - Number (%)
<1	0 (0.00)	5 (7.2)
1-5	1 (3.2)	19 (27.5)
6-10	4 (12.9)	22 (31.9)
11-15	5 (16.1)	13 (18.8)
16-20	11 (35.5)	6 (8.7)
21-25	2 (6.5)	1 (1.4)
>25	8 (25.8)	3 (4.3)
Total	31 (100.0)	69 (100.0)
Mean ± SD	18.63 ± 8.17	9.22 ± 6.73
Range	4.00 - 40.00	0.30 - 28.00

T value = 2.295, *p* value = 0.024 (<0.05) (S)

The data of induction to pain interval (IPI) in relation to parity presented in the Table 8 shows that the primigravida has a shorter induction pain interval compared to multigravida with mean and standard deviation 9.68 ± 7.20 and 14.58 ± 8.82 respectively.

Table 8: Induction to pain interval (IPI) in relation to parity

IPI (hrs)	Primigravida- Number (%)	Multigravida- Number (%)
<1	4 (8.0)	1 (2.0)
1-5	13 (26.0)	7 (14.0)
6-10	13 (26.0)	13 (26.0)
11-15	12 (24.0)	6 (12.0)
16-20	5 (10.0)	12 (24.0)
21-25	0 (0.00)	3 (6.0)
>25	3 (6.0)	8 (16.0)
Total	50 (100.0)	50 (100.0)
Mean ± SD	9.68 ± 7.20	14.58 ± 8.82

Chi square = 13.755, *p* value = 0.032 (<0.05) (S)

The data of the induction delivery interval (IDI) in relation to gestational age presented in the Table 9 shows that 50% of the cases in T2 group delivered within 21-30 hours whereas, 80% of the cases in T3 group delivered within 20 hours. The mean induction delivery interval for T2 group is 24.94 ± 8.23 and T3 group was 15.67 ± 9.64. The *p* value is 0.307 which is statistically not significant.

Table 9: Induction delivery interval (IDI) in relation to gestational age

IDI (hrs)	Gestational age	
	T2 - Number (%)	T3 - Number (%)
1-10	0 (0.00)	29 (42.0)
11-20	9 (29.0)	26 (37.7)
21-30	15 (48.4)	9 (13.0)
31-40	6 (19.4)	2 (2.9)
>41	1 (3.2)	3 (4.3)
Total	31 (100.0)	69 (100.0)
Mean ± SD	24.94 ± 8.23	15.67 ± 9.64
Range	12 - 48.50	3.55 - 48.00

T value = 1.02; *p* value = 0.307 (>0.05) (NS)

The data of the induction delivery interval (IDI) in relation to parity is presented in Table 10. In this study the induction delivery interval in primigravida was lesser compared to multigravida with a mean 16.70 ± 10.38 and 20.38 ± 9.65 respectively. Statistical analysis data (*p* value 0.024) is statistically significant.

Table 10: Induction delivery interval (IDI) in relation to parity

IDI (hrs)	Primigravida	Multigravida
	Number (%)	Number (%)
1-10	20 (40.0)	9 (18.0)
11-20	17 (34.0)	18 (16.0)
21-30	9 (18.0)	15 (30.0)
31-40	1 (2.0)	7 (14.0)
>40	3 (6.0)	1 (2.0)
Total	50 (100.0)	50 (100.0)
Mean ± SD	16.70 ± 10.38	20.38 ± 9.65

Chi square = 11.201, *p* value = 0.024 (<0.05) (S)

The data of the Induction delivery interval (IDI) in relation to modified Bishop score is presented in the Table 11. Induction delivery interval is lesser in ripe cervix (Modified Bishop Score 6-9) as compared to unripe cervix (Bishop score 0-5). The mean IDI was 22.48 ± 9.19 in unripe cervix and 12.11 ± 8.21 in ripe cervix. The *p* value 0.000 is statistically highly significant.

Table 11: Induction delivery interval (IDI) in relation to Modified Bishop score

IDI (hrs)	Modified Bishop score	
	Unripe cervix (0-5)	Ripe cervix (6-9)
<1	0 (0.00)	3 (7.9)
1-10	5 (8.1)	21 (55.3)
11-20	10 (16.1)	5 (13.2)
21-30	18 (29.0)	5 (13.2)
31-40	16 (15.8)	2 (5.3)
>40	13 (21.0)	2 (5.3)
Total	62 (100.0)	38 (100.0)
Mean ± SD	22.48 ± 9.19	12.11 ± 8.21

T value = 5.69, *p* value = 0.000 (<0.05) (HS)

In this study the data of mode of delivery and Oxytocin augmentation presented in the Table 12 shows that all the n = 100 subjects delivered vaginally. Oxytocin augmentation was required in 1 subject in T2 group and 16 cases in T3 group. This shows that more cases in T3 group required oxytocin augmentation.

Table 12: Mode of delivery

Mode of delivery	Number (%)
FTVD	27 (27.0)
PTVD	42 (54.00%)
Complete abortion	31 (31.0)
Total	100
Oxytocin augmentation	
Gestational age	
T2	1 (3.22)
T3	16 (23.18)

The data of failed induction of labour in the present study subjects present in Table 13 shows that the failed induction in 2nd trimester is 35.48% whereas, in the 3rd trimester it is recorded 7.24%. Hence, the success rate in 2nd trimester is 64.52% whereas, in 3rd trimester, it is observed 92.76%.

Table 13: Success rate and failed Induction

Gestational age	Failed induction- Number (%)	Success rate- Number (%)
T2	11 (35.48)	20 (64.52)
T3	5 (7.24)	64 (92.76)
Total	16	84

In the failure cases, alternative methods of induction were used as represented in Table 14. All the cases of failed induction delivered vaginally.

Table 14: Alternate methods used

Alternate method	T2- Number (%)	T3- Number (%)
Oxytocin	4 (12.9)	4 (5.8)
Mifepristone	2 (6.5)	0 (0.00)
Cerviprime	2 (6.5)	1 (1.4)

Chi square = 16.294, *p* value = 0.001 (<0.05) (HS)

The data of the incidence of adverse effects is comparatively more in T3 group than in T2 group in this study as represented in the Table 15. All these adverse effects were treated symptomatically.

Table 15: Adverse effects

Adverse effects	T2- Number (%)	T3- Number (%)
Fever	3 (9.6)	12 (17.3)
Nausea, Vomiting	4 (12.9)	7 (10.14)
Diarrhoea	-	2 (2.8)
Total	7 (22.5)	21 (30.24)

The data of the maternal complications of the present study subjects presented in the Table 16 shows that tachysystole was observed in 2.8% subjects in T3 group, whereas, it was found in 9.6% cases in T2 group. The cases in T3 group with tachysystole required total dose of Misoprostol more than 200 µgm, whereas all the cases in T2 required more than 350 µgm. This shows that tachysystole occurred when increased total dosage of Misoprostol was used.

Table 16: Maternal complications – Tachysystole

Gestational age	Tachysystole- Number (%)
T2	3 (9.6)
T3	2 (2.8)
Total	5 (12.4)

Discussion

The present study consisted of n = 100 subjects of pregnant ladies complicated with intrauterine fetal death. They were divided into two groups - Second and Third trimester pregnancies (T2 and T3). Both groups received Misoprostol, starting from a dose of 25 µg up to maximum of 6 doses. When the first dose did not lead to any effective uterine contractions, the subsequent dose was doubled to 50 µg and then to 100 µg after 4 hours of the last dose.

The studies have demonstrated that, the optimal Intravaginal dose of Misoprostol is 25 µg taken every 4-6 hours. Higher doses or shorter dosing intervals are associated with a higher incidence of side effects and complications like Tachysystole / Hyperstimulation syndrome.

The current study investigation was conducted to assess the effectiveness of vaginal Misoprostol in termination of second and third trimester pregnancies complicated with intra uterine fetal death.

In the earlier study reports, the mean and total dose of Misoprostol used in T3 group is lesser compared to T2 group [1, 7-10]. The results of these studies are consistent with the observations made in the present study.

The present study results showed that the mean induction pain interval in primigravida is lesser compared to multigravida contradictory to the reported results earlier [1, 9]. The study conducted by El- Gharib *et al.* [1] showed the presence of inverse correlation between parity and induction pain interval contradictory to the results of the present study observations.

In the present study the inverse relation between gestational age and induction pain interval is well established which is comparable to the studies made earlier [1, 9]

The studies conducted by EL- Gharib *et al.* [1] showed that the induction delivery interval in multigravida is comparatively lesser than the primigravida, however the present study observations does not correlate with these results i.e., the mean induction delivery interval in primigravida is lesser than multigravida.

The mean induction to vaginal delivery interval was 24.94 ± 8.23 in T2 group compared to 15.67 ± 9.64 in T3 group and is statistically significant. The present study results are consistent with the results of the above mentioned studies.

The inverse relationship between gestational age and induction delivery interval has been confirmed in this study. Furthermore, another significant negative correlation between gestational age and induction pain interval, induction delivery interval and total required dose of Misoprostol is well established in this study which correlates with earlier studies [1, 7].

This study also proves that the induction delivery interval is less with a ripe cervix (modified Bishop score ≥ 6) than the unripe cervix (0-5). Similar results were reported earlier in the study conducted by Nakintu *et al.* [7].

The vaginal delivery within 24 hours of induction i.e., 24 hours from the administration of first dose of Misoprostol is considered successful. The success rate was 92.76% in T3 group compared to 64.52% in T2 group which is statistically significant. This again proves that as the gestational age advances there is shorter induction delivery interval. This result agrees with the results reported earlier [1, 14].

The oxytocin augmentation in T3 is significantly higher than T2 group in this study. This is contradictory to the earlier study results recorded [1, 8].

In this study, the incidence of adverse effects is more in T3 group than in T2 group. Upto 80% of these cases in both T2 and T3 groups had an induction delivery interval of >20 hours and the total dose of Misoprostol administration was more than 300 µg. The study of El-Gharib *et al.* [1] says that all side effects occurred after an induction delivery interval of ≥ 34 hours.

Tachysystole in this study is considered when there were ≥6 uterine contractions in 10 minute period. Tachysystole was observed in 2.8% of cases in T3 group whereas 9.6% cases in T2 group. The total dose required for T3 and T2 groups were 25-150 µg and 150-450 µg of Misoprostol respectively. This shows that tachysystole occurred when total dose of Misoprostol is increased.

Other complications like premature separation of placenta, postpartum haemorrhage and rare events such as uterine rupture or amniotic fluid embolism did not occur in this study.

Mode of delivery

All patients in this study delivered vaginally. For all the failed induction cases, alternate method of induction was used, for most of the cases oxytocin infusion was used. All these cases delivered vaginally.

The success rate was lesser in T2 group as compared to T3 group which is statistically significant. This indicates that as the gestational age advances, prompt response to low dose Misoprostol is seen. Placenta in all the cases expelled completely.

Conclusion

The present study concludes that low dose Misoprostol is a safe, effective, practical and inexpensive method for termination of 3rd trimester pregnancies compared to 2nd trimester pregnancies complicated with intrauterine fetal death. The effect of Misoprostol increases with duration of gestation.

References

1. El-Gharib MN, El-Ebyary MT, Alhawary TS, Elshourbagy SH. Low dose vaginal misoprostol in the management of women with intrauterine fetal death. Clinical Medicine insights: Women's Health 2010;3:15-21.
2. Rodolfo G, Wing D, Christian F. WHO misoprostol guidelines. Draft 2/11/07, chapter 8: Page. 1-8.
3. Jodie MD, Caroline AC. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database of Systematic Review 2010;4:1-11.
4. Miriam Z, Susan KF, Neal LB, Deborah B, Philip DD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstetrics & Gynecology 1997;90(l):88-91.
5. Raghavan KS. Prostaglandins in labour. Chapter-13, 1st Edn. Management of labour. Edt - S. Arulkumaran SS. Rathnam and K. Bhaskar Rao, 2001, 197-212.
6. Michael WB, Nancy K, Ken L, Alain G, Marie FD, Francine T. A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination. Am J Obstet Gynecol 2002;187(4):853-857.
7. Nakintu N. A comparative study of vaginal misoprostol and intravenous oxytocin for induction of labour in women with intrauterine fetal death in Mulago I Hospital, Uganda. African Health Sciences 2001;1(2):55-59.
8. Ezechi OC, Kalu Bke, Ndububa VI, Nwokoro CA. Induction of labour by vaginal misoprostol for intrauterine fetal death. J Obstet Gynecol Ind 2004;54(6):561-563.
9. Carlan CJ, Danielle B, William F, O' Brien. Buccal versus intravaginal misoprostol administration for cervical ripening. Am J Obstet Gynecol 2002;186:229-233.
10. Srisomboon J, Pongpisuttinum S. Efficacy of intracervicovaginal misoprostol in second-trimester pregnancy termination: a comparison between live and dead fetuses. Journal of Obstet Gynaecol Res 1998;24(1):l-5.
11. Nyende L, Towobola OA, Mabina MH. Comparison of vaginal and oral misoprostol for the induction of labour in women with intra-uterine foetal death. East African Medical Journal 2004;81(4):179-182.
12. David A, Jonathan WW, Scott B, Michael E. Oral or vaginal misoprostol administration for induction of labour: A randomized, double-blind trial. Obstet Gynecol 1998;92(5):810-813.
13. Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labour induction. Am J Obstet Gynecol 1997;176:1423.
14. Bugalho A, Bique C, Almeida L, Bergstorm S. Application of vaginal misoprostol before cervical dilatation to facilitate first trimester pregnancy interruption. Obstet Gynecol. 1994;183:729.