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## Original Research Article

# Study of vaginal misoprostol for labour induction in intra uterine fetal demise

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### ABSTRACT

**Background:** Intrauterine fetal demise (IUFD) is the most undesirable consequence of pregnancy which causes psychological distress to mother and family. It also carries risk of infection and DIC. In literature, various methods have been described to manage the cases of IUFD. Practically prostaglandin analogues are routinely used for induction of labour in cases of IUFD. The objectives of this study were to assess the effectiveness and safety of vaginal misoprostol for induction of labour in IUFD.

**Methods:** In this prospective study, consecutive series of 100 women with IUFD  $\geq 28$  weeks of gestation are studied. Detailed clinical history, physical examination and investigations are recorded. All selected cases were induced with vaginal misoprostol 50  $\mu$ g and the doses are repeated every 6th hourly depending on uterine contractions and Bishop's score changes.

**Results:** The average induction to delivery interval is 14.68 hours. All women delivered within 40 hours of administration of first dose of misoprostol with 47%, 86% and 100% delivering within 12 hours, 24 hours and 40 hours respectively. There was significant correlation between mean induction delivery interval and maternal age, parity and Bishop's score. Minor side effects like chills and fever were noted in 5% of patients and retained placenta and atonic PPH was seen in 2% each.

**Conclusions:** The low dose vaginal misoprostol for induction of labour in IUFD is a safe, effective and cost effective regimen.

**Keywords:** Bishop's score, Induction of labour, IUFD, Misoprostol

### INTRODUCTION

The death of a formed fetus is one of the most emotionally devastating events for mother and clinicians. When a baby dies in utero the options are either to wait for labour to start spontaneously or to induce the labour. About 80% of women will deliver within 3 weeks of fetal death. But if fetal death occurs in utero without expulsion for several weeks then such retention of the fetus is associated with emotional distress and grief reaction which may be severe. If the rupture of fetal membranes occurs the risk of intrauterine infection increases and also there is a time related risk of consumption coagulopathy.<sup>1</sup>

This may have implications for counseling about the risks and management for any future pregnancies.<sup>2</sup> In modern obstetrical practice medical induction of labor is recommended in case of intra uterine fetal demise. The use of oxytocin for induction of labour in IUFD is often difficult, painful and less successful especially in cases of early gestation, as uterus is less sensitive to oxytocin before term. The availability of prostaglandins has facilitated delivery options for patients with fetal deaths especially in the presence of unfavorable cervix. Misoprostol, a synthetic prostaglandin E1 analogue, has been found to be safe and effective for induction of labour in cases of IUFD. Its cost effectiveness, stability at

room temperature and ease of availability and administration makes it an ideal drug for induction in cases of IUFD. Vaginal misoprostol is very effective because peak levels are reached slowly and sustained for long duration of time. It also has the advantage of less gastrointestinal side effects and greater bioavailability as compared to other routes of administration. This active approach will virtually eliminate the possibility of infection and consumptive coagulopathy and to some extent psychological stress involved in IUFD.

## METHODS

In this prospective study, a consecutive series of 100 women with intrauterine fetal demise  $\geq 28$  weeks of gestation during the period of 1<sup>st</sup> August 2012 to 30<sup>th</sup> July 2014 are studied. Study was conducted on patients who are admitted in Department of Obstetrics and Gynecology, VIMS, Bellary. All women were counseled regarding induction and options available for induction. All advantages and disadvantages of induction methods, complications and side effects of drug were also explained. All cases were subjected to detailed history taking and clinical examination. Ultrasound confirmation of intra uterine fetal demise was obtained. Consent was taken after counseling the patients. Patients were administered misoprostol 50 $\mu$ g in the posterior fornix. The dose is repeated every 6th hourly depending on changes in Bishop's score and uterine contraction. If the Bishop's score is more or equal to eight or if the contractions are  $>2$  in ten minutes lasting for  $\geq 40$  seconds, then no further doses of misoprostol were administered. A maximum of six doses were allowed to administer. The side effects like gastrointestinal side effects, shivering and fever which occurred during induction were noted.

Also complications like retention of placenta, PPH or placental abruptions were noted. The need for surgical intervention for removal of the placenta or any other medical intervention used were documented. If delivery does not occur after this regimen, then based on clinical situation appropriate method was used for termination of pregnancy. Any complications during period of induction and till 24 hours after delivery were reported. Routine antibiotics were given during the course of induction and after delivery. Patients were discharged after 24 hours of delivery or later depending on clinical condition of the patient. The data like maternal age, parity, gestational age, Bishop's score, birth weight, induction to delivery interval were analyzed using the SPSS 20 for windows statistical package. Variables that were normally distributed are presented as means with standard deviation and ranges. For assessment of correlations between multiple variables and induction delivery interval multiple regression analysis was used. The induction to delivery interval was used as the dependent variable subsequent to log transformation. Differences were regarded as statistically significant if P value  $<0.05$ .

## RESULTS

In present study we studied 100 consecutive women with intra uterine fetal demise after 28 weeks of gestation who are induced with vaginal misoprostol 50 $\mu$ g during the period of 1<sup>st</sup> August 2012 to 31<sup>st</sup> July 2014. The patient characteristics are as follows:

**Table 1: Age wise distribution.**

Age group	Frequency	Percent
Up to 20 years	26	26.0
21 - 25 years	47	47.0
26 - 30 years	24	24.0
31 - 35 years	3	3.0
Total	100	100.0

The age group ranged from 18 years to 35 years. The mean age was 23.64 years. Majority of women (47%) were in the age group of 20 to 25 years.

**Table 2: Distribution based on obstetrics score.**

Obstetrics score	Frequency	Percent
Primi gravida	39	39.0
Multi gravida	61	61.0
Total	100	100.0

In our study 39 women were primigravidas and 61 were multigravida.

**Table 3: Distribution based on gestational age.**

Gestational age	Frequency	Percent
28 - 32 weeks	51	51.0
33 - 36 weeks	14	14.0
37 - 40 weeks	31	31.0
41 - 43 weeks	04	04.0
Total	100	100.0

The average gestational age was 33.8 weeks, ranging from 28 weeks to 43 weeks. Majority of the patient were (51%) in 28 -32 weeks of gestation. In 100 cases 65 were preterm, 31 patients were belonged to 37-40 weeks of gestation, 4 patients were with prolonged pregnancy.

**Table 4: Distribution based on Bishop's score.**

Bishops score	Frequency	Percent
1	13	13.0
2	34	34.0
3	40	40.0
4	13	13.0
Total	100	100.0

Bishops score was determined before inducing with misoprostol. In our study Bishop's score ranged from 1 to 4 and the mean Bishop score was 2.53.

**Table 5: Distribution based on total dose of misoprostol.**

Doses	Frequency	Percent
1 = 50µg	29	29.0
2 = 100µg	31	31.0
3 = 150µg	19	19.0
4 = 200µg	10	10.0
5 = 250µg	5	5.0
6 = 300µg	6	6.0
Total	100	100.0

Majority of the women delivered with 1 to 2 doses of misoprostol (60%). Among 100 cases 29 women delivered with 1 dose of misoprostol, 31 with 2 doses, 19 with 3 doses, 10 with 4 doses, 5 with 5 doses and 6 patients required total 6 doses to deliver.

**Table 6: Distribution based on side effects.**

Side effects	Frequency	Percent
Nil	91	91.0
Atonic PPH	2	2.0
Chills	1	1.0
Post-partum pyrexia	4	4.0
Retained placenta	2	2.0
Total	100	100.0

There were no side effects seen in 91% of cases. Post-partum fever was seen in 4 cases and chills was seen in one case. Two patient had atonic PPH which was treated with uterotonics. There was retained placenta in 2 cases which were removed manually. None of the cases had uterine hyper tonicity or tachysystole. No gastrointestinal side effects were seen.

**Table 7: Distribution based on induction delivery interval in hours.**

IDI	Frequency	Percent
Up to 6 hours	10	10.0
6 - 12 hours	37	37.0
12 - 18 hours	24	24.0
18 - 24 hours	15	15.0
>24 hours	14	14.0
Total	100	100.0

- Minimum induction to delivery interval is 4 hours
- Maximum induction to delivery interval is 38 hours 40 minutes
- Mean induction to delivery interval is 14 hours 68 minutes.

All women delivered vaginally, the success rate of this regimen is 100%. Forty seven percent of women delivered within 12 hours, 86% of women delivered within 24 hours and 100% women delivered within 40 hours of initiation of induction.

Multiple regression analysis is used to compare the different factors that may affect induction to delivery interval.

**Table 8: Relation between induction delivery interval in minutes and maternal age.**

Age group	Mean	Number	Standard deviation
Up to 20 years	1119.73	26	550.40
21 - 25 years	841.87	47	536.53
26 - 30 years	735.50	24	355.37
31 - 35 years	812.33	3	458.83
Total	887.70	100	514.56

P value - 0.001.

The maternal age ranged from 18 to 35 years. In our study, significant correlation was found between induction to delivery interval and maternal age (P = 0.001). We observed that induction delivery interval decreases as maternal age increases. This may be due to increase in parity of women as age advances.

**Table 9: Relation between induction delivery interval and obstetrics score.**

Induction delivery interval	Obstetrics score		Total
	Primi	Others	
Up to 6 hours	1 (2.6%)	9 (14.8%)	10 (10.0%)
6 - 12 hours	10 (25.6%)	27 (44.3%)	37 (37.0%)
12 - 18 hours	6 (15.4%)	18 (29.5%)	24 (24.0%)
18 - 24 hours	13 (33.3%)	2 (3.3%)	15 (15.0%)
>24 hours	9 (23.1%)	5 (8.2%)	14 (14.0%)
Total	39 (100.0%)	61 (100.0%)	100 (100.0%)

P value - 0.001.

In our study 11% of primigravidas delivered within 12 hours as compared to 36% of multigravidas. 40% of primigravidas delivered within 24 hours as compared to 56% of multigravidas. 23% of primigravidas took >24 hours to deliver as compared to 8.2% of multigravidas.

**Table 10: Comparison of mean induction delivery interval to obstetric score.**

Obstetrics score	Number	Mean (minutes)	Standard deviation	Standard error of mean
Primi	39	1131.36	544.95	87.26
Others	61	731.92	430.73	55.15

P value - 0.01.

The mean induction to delivery interval in multigravidas was 12.1 hours and in primigravidas was 18.8 hours. Mean induction delivery interval was less in multigravidas as compared to primigravida and this was statistically significant in our study (P = 0.01).

**Table 11: Comparison of mean induction delivery interval to gestational age.**

Gestational age	Mean	Number	Std. deviation
28 - 32 weeks	814.33	51	429.47
33 - 37 weeks	1077.05	19	645.50
>37 weeks	892.50	30	542.47
Total	887.70	100	514.56

P value - 0.16.

The gestational age ranged from 28 to 43 weeks. The mean gestational age was 33.84 weeks. The induction to delivery interval and gestational age were correlated and found that there was no significant correlation between mean induction to delivery interval and gestational age ( $P = 0.16$ ).

**Table 12: Comparison of mean induction delivery interval to total dose of misoprostol.**

Total dose	Mean	Number	Std. deviation
1.00	410.00	29	88.24
2.00	695.87	31	117.48
3.00	1014.26	19	164.61
4.00	1400.00	10	122.34
5.00	1792.00	5	135.90
6.00	2179.50	6	138.11
Total	887.70	100	514.56

P value - 0.03.

There was significant correlation between mean induction delivery interval and total dose of misoprostol used ( $P = 0.03$ ).

### Induction to delivery interval and Bishop score relation

The mean bishop score in our study group was 2.53 and ranged from 1 to 4. Bishop score does affect the mean induction to delivery interval and is statistically significant ( $P = 0.03$ ).

Our low dose vaginal misoprostol regimen had 100% success rate with a mean induction to delivery interval of 14.68 hours. This interval is affected by age of the patient, parity and Bishop's score. But gestational age and uterine size does not seem to affect induction delivery interval. This regimen is well tolerated and had minor side effects like fever and chills in 5% of cases, 2% women required manual removal of placenta and atonic PPH was seen in 2% of cases.

### DISCUSSION

Several methods of induction of labor following late IUFD have been described in literature. Our study was aimed to see the effectiveness of low dose vaginal misoprostol for induction of labour in case of IUFD after 28 weeks of gestation and to compare this to other described regimen in the literature and to assess how our regimen performs among our population. In our study we used the dose regimen of vaginal misoprostol 50µg every 6th hourly up to maximum of 6 doses. All the women in our study group delivered vaginally with the mean induction to delivery interval of 14.68 hours. Our study showed that this regimen is very effective and safe method to induce labor in late IUFD with minimal side effects. As this regimen is cost effective, it is also suitable for our socio economical set up.

**Table 13: Average IDI of different regimens using misoprostol.**

Reference study	Gestational age (weeks)	Regimen	Induction to delivery interval (hours)
Draycott et al <sup>3</sup>	24-41	100 µg PV maximum of 6 doses	10
Fletcher et al <sup>4</sup>	24-40	100 µg PV, 24 <sup>th</sup> hourly	11.9
Bulgaho et al <sup>5</sup>	18-40	100 µg PV, 12 <sup>th</sup> hourly	12.6
L.Nynde et al <sup>6</sup>	20-41	200 µg 6 <sup>th</sup> hourly PV maximum 4 doses	13.5
Ezechi et al <sup>7</sup>	>28	100 µg PV 12 <sup>th</sup> hourly	14.18
Srisomboon et al <sup>8</sup>	14-28	1 200 µg, 12 hrly PV	15
Marian Neto et al <sup>9</sup>	19-41	400 µg PV 4 <sup>th</sup> hourly	17.6
Chittareon A et al <sup>10</sup>	16-41	200 µg PV 12 <sup>th</sup> hourly	18.8
Maria Isabel de et al <sup>11</sup>	>22	50-400 µg 6-12 hrly	20.1
EL.Gharib et al <sup>12</sup>	20-41	25µg 4 <sup>th</sup> hourly maximum 6 doses	21
MA.Abdul et al <sup>13</sup>	>14-20	400µg 12 <sup>th</sup> hrly	15.1
	20-26	200µg 12 <sup>th</sup> hrly	9.2
	>28	50µg 6 <sup>th</sup> hrly maximum 4 doses	18.5
Our study	>28	50 µg, every 6 <sup>th</sup> hourly PV	14.68

In our study the mean induction to delivery interval was 14.68 hours. This was comparable to previous studies using different dose regimen of vaginal misoprostol. The observation shows that higher and frequent doses of misoprostol decreases induction to delivery interval.

Bugalho et al found a quicker uterine response in women with more advanced gestation. Study done by EL.<sup>5</sup> Gharib et al, and Ezechi et al also shows that induction delivery interval is inversely proportional to gestational age.<sup>7,12</sup> Uterine sensitivity to misoprostol is known to increase with advancing gestation.

We had 30 patients with gestation of 37 weeks or more and mean induction to delivery among these women was 14.8hrs hours, 19 patients with gestation of 33-37 weeks had mean induction to delivery interval of 17.9 hours and 51 patients with 28-32 weeks of gestation had mean induction to delivery interval of 18.5 hours. With this observation it appears that induction to delivery interval decreases with advanced gestation, but when multiple regression analysis was used we found no significant correlation between mean induction to delivery interval and gestational age (P- 0.16).

**Table 14: Mean maternal age and mean induction delivery interval.**

Study	Maternal age (years)	Mean Induction to delivery interval (hours)
EL.Gharib et al <sup>12</sup>	25.5	21
Maria Isabel de et al <sup>11</sup>	26.1	20.1
L.Nynde et al <sup>6</sup>	26.4	13.5
MA.Abdul et al <sup>13</sup>	26.7	14.6
Ezechi et al <sup>7</sup>	27.1	14.18
Our study	23.65	14.68

Induction delivery interval decreases as maternal age increases. This may be due to increase in parity of women as age advances. In our study significant correlation was found between induction to delivery interval and maternal age (P = 0.001). This trend of decrease in induction delivery interval with maternal age was also seen in other studies.

**Table 15: Misoprostol dose and side effects.**

Study	Dose	Gastro intestinal effects	Other minor side effects (fever, chills)	Retention of placenta	PPH	Total Side effects	Induction delivery interval (hrs)
EL.Gharib et al <sup>12</sup>	25µg 4 <sup>th</sup> hourly	15%	5%	5%	-	30%	21.36
Maria Isabel de et al <sup>11</sup>	50-400 µg 6-12 hrly	5%	2%	31.4%	2%	40%	20.1
Gomez et al <sup>14</sup>	50 µg 4 <sup>th</sup> hourly PV	35%	7%	-	-	42%	15.2
MA.Abdul et al <sup>13</sup>	50 µg 6 <sup>th</sup> hourly PV	14%	-	4%	-	18%	14.6
Ezechi et al <sup>7</sup>	100 µg 12 <sup>th</sup> hourly	2.7%	2%	5.4%	8%	19%	14.18
L.Nynde et al <sup>6</sup>	200 µg 6 <sup>th</sup> hourly	15%	5%	-	-	20%	13.5
Our study	50 µg 6 <sup>th</sup> hourly	-	5%	2%	2%	9%	14.68

Our regimen carried no gastrointestinal side effects like nausea, vomiting or diarrhoea, but in 5% cases minor side effects like fever, chills were noted. Retained placenta was another complication which was noted in 2% of the cases in our study. These cases were managed by manual removal of placenta. This has been observed in other studies also and rate of placental retention was observed more with lesser gestational age. Two cases in the study group had atonic post-partum haemorrhage (2%) which was controlled by uterotonics. In our study we did not encounter any women with uterine tachysystole or hypertonic uterine contraction because of usage of low dose of the drug. The side effects rate of our study is 9% which is less compared with previous studies. So by using low dose misoprostol we can achieve delivery within reasonable time period with significantly less side effects.

In Bulgaho et al, study the success rates ranged from 67% to 100%. Gharib EL et al, study had success rate of 90%. Our study has success rate of 100%.<sup>5,12</sup>

The side effects can be minimized by vaginal administration of relatively low dose. The side effects and the requirement of dose of misoprostol can also be reduced by using oxytocin along with it.

## CONCLUSION

The low dose vaginal misoprostol is a safe and effective method for induction of labor following IUFD after 28 weeks of gestation. The induction to delivery interval is shorter with lesser side effects. But further studies are needed to determine the optimum dose of misoprostol.



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