Preinduction cervical ripening with vaginal misoprostol in second and third trimester intrauterine fetal demise

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ABSTRACT

Aims: To study the effectiveness of vaginal misoprostol according to the FIGO 2017 guideline for preinduction cervical ripening in second and third trimester pregnancy with intrauterine fetal demise.

Methods: During six months period from October 2017 to April 2018 at Paropakar Maternity and Women's Hospital, Thapathali, Kathmandu, Nepal, cases admitted for second and third trimester termination of pregnancy for fetal demise were studied using the International Federation of Gynaecology and Obstetrics (FIGO) recommended doses of vaginal misoprostol. For gestational age of 13-26 weeks 200µg, for 27-28 weeks dose of 100µg and for >28 weeks dose of 25µg, every 6 hours was used. Main outcome measured included change in modified Bishop Score, insertion of first dose of vaginal misoprostol to delivery interval and maternal side effects.

Results: In this study including 54 cases, mean preinduction Bishop score was 2.12. Bishop score remained unchanged in 2 cases, 28 had score between 4 to 6, 10 cases had score between 7 to 8 and 14 cases had Bishop score more than 8. The change in Bishop Score is statistically significant (p=0.007). 50 cases had vaginal delivery and it occurred within 19.83±13.1 hours. It took minimum 3 hours to maximum 52 hours from the first dose of misoprostol to delivery of the fetus. No side effects were noted within 24 hours of the last dose of vaginal misoprostol.

Conclusions: Vaginal misoprostol according to FIGO guideline 2017 is safe and effective for preinduction cervical ripening in second and third trimester intrauterine fetal demise leading to successful vaginal delivery.

Keywords: cervical ripening, FIGO, IUFD, misoprostol

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INTRODUCTION

Intrauterine fetal demise is a heartbreaking event in life of an expecting woman. So, curtailing the waiting period by labour induction is a preferable intervention to alleviate the anxiety associated with it. Cervical ripening can be done by pharmacological or mechanical techniques for unfavourable cervix for induction of labour. Induction implies stimulation of contraction before spontaneous onset of labour, with or without ruptured membranes.[1] The favourability of cervix is determined with Bishop score or modified Bishop scoring system.[2] Prostaglandins are the recent and well accepted drug for cervical ripening and labour induction in pregnant women with an unfavourable cervix. Misoprostol, the newer prostaglandin-E_1 is a synthetic 15-deoxy-16hydroxy-16 methyl analogue of naturally occurring prostaglandin and has been widely used for labour induction due to its efficacy, low cost and stability at room temperature with a shelf life of three years. It leads to myometrial contraction in the pregnant uterus by binding to EP2/EP3 prostaglandin receptors. Studies showed misoprostol to be more effective than dinoprostone for inducing labour and were associated with lower Cesarean rate.[3] Vaginal administration results in slower increase and lower peak plasma concentration of active metabolite than the oral administration. But overall exposure to the drug and duration of exposure is increased with vaginal administration. The guidelines for the use

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of misoprostol in termination of second and third trimester intrauterine fetal demise are limited; hence this study was conducted to assess the safety and efficacy of misoprostol according to FIGO guideline[4] for preinduction cervical ripening.

METHODS

This is a cross sectional study, evaluating the effectiveness of vaginal misoprostol according to the FIGO-2017 guideline for termination of pregnancy in second and third trimester intrauterine fetal demise conducted from October 2017 to April 2018 at Paropakar Maternity and Women's hospital, Thapathali, Kathmandu, Nepal.

Sonography proven singleton intra-uterine fetal death not in labor were taken by excluding factors contraindicating induced vaginal delivery. According to the FIGO 2017 guideline[4], 200µg, 100µg and 25µg of Misoprostol was kept vaginally for 13-26 weeks, 27-28 weeks and >28 weeks of gestation respectively; and it was repeated 4 hourly for 27-28 weeks and 6 hourly for other two groups until the modified Bishop score was ≥4 or uterine contraction was established. Thereafter the labor was proceeded as per status. The total doses of misoprostol required, mode of delivery, misoprostol to delivery interval and maternal complications noted if any. SPSS 16 used and descriptive results obtained.

RESULTS

Total of 54 (30.3%) cases fulfilled the selection criteria from 178 cases of still births in 6 months; 72% fell in 20-29 years age group [Table-1]. Third trimester IUFD was the highest one by 63% [Figure-1].

Table-1: Distribution of cases according to age group in years (n=54)

Age Group	Frequency	%
15-19	5	9.3
20-24	23	42.6
25-29	16	29.6
30-34	8	14.8
35-39	1	1.9
>39	1	1.9

Mean initial Bishop score was similar to all gestational age group and 6 or more in 6 hours [Figure-2].

The study shows that 33.3% (n=18) of cases had successful priming with single dose. Maximum number of doses required for cervical change was 8 which were for 2 (3.7%) cases. 32 cases required 2-5 doses. Two cases didn't respond to the drug. The difference was statistically significant (p=0.007) [Table-2].

Table-2: Total number of vaginal Misoprostol received and change in Bishop score (n=52)

Total No of Doses given to patient	Unchanged	Change in Bishop Score			Frequency (%)
		4-6	7-8	>8	
1	1	7	4	7	18 (33.3%)
2	0	8	4	3	15 (27.8%)
3	0	5	0	1	6 (11.1%)
4	0	4	0	1	5 (9.3%)
5	0	3	1	2	6 (11.1%)
8	0	1	1	0	2 (3.7%)
9	1	0	0	0	0
					52 (96.3%)

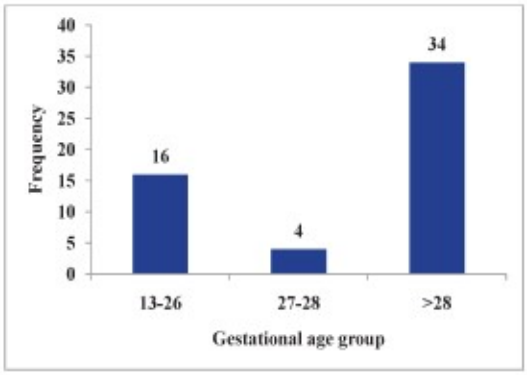

Figure-1: Distribution of IUFD by gestational age group (n=54)

Among 54 cases, 50 cases had vaginal delivery which occurred within 19.83±13.1 hours. It took minimum 3 hours to maximum 52 hours from the first dose of misoprostol to delivery. Mean duration of first insertion of misoprostol to delivery was 21.7±13.9 hours, and it was not statistically significant by gestational age group category [Table-7]. However the duration of insertion to delivery was affected by the parity of the patient (p=0.01). The analysis shows that duration between cervical ripening and delivery is affected by gravidity as well (p=0.005).

In 54 cases 92.6% (n=50) had vaginal delivery which is statistically significant (p=0.00). Other 4 cases

had operative delivery; 1 hysterotomy (1.9%) from 200**µg** group due to antepartum haemorrhage which was intraoperatively found to be due to undiagnosed placenta previa. Among 3 Cesarean Sections 1 was done for suspected uterine rupture after receiving 2 doses of 25**µg** of misoprostol. However, intraoperatively no uterine rupture was present. Another case underwent Cesarean Section for failed induction of labour (1.9%) after receiving 9 doses of 25**µg** of misoprostol. Third case underwent Cesarean Section as cervical cancer was suspected during reassessment. No side effects were noted within 24 hours of last dose of vaginal misoprostol.

Table-7: Insertion to delivery interval by period of gestation (n=50)

Gestational weeks	N	Mean Duration in hours	Std. Deviation	p-value
13-26	15	20.60	15.26	0.513
27-28	4	28.50	10.66	
>28	31	21.36	13.72	
Total	50	21.70	13.89	

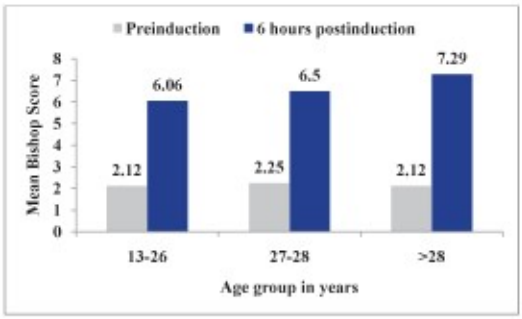

Figure-2: Initial Modified Bishop Score pre and post induction (n=54)

DISCUSSION

Misoprostol has been proved as an effective drug for pre-labour cervical ripening and the FIGO guideline for use of Misoprostol, 2017, has been proposed after many studies. Majority of women with IUFD belonged to age group of 22-24 years (n=23, 42.6%) and second highest amongst age group of 25-29 years (n=16, 29.6%). Similar results were reported by Patel et al in their study where 47.3% IUFD occurred in age group 21-25 years and 37.5% in 26-30 years.[5] However, Man et al reported that women in whom an intrauterine death occurs were significantly older than the overall obstetric population; and that the risk of fetal loss in relation to increased maternal age is similar across the second and third trimesters and is not limited to third-trimester stillbirth.[6]

The change in Bishop score is statistically significant (p=0.007) in this study. Due to the paucity of literature on doses of Misoprostol according to FIGO 2017, the exact comparison has been difficult but the results can still be compared. Das et al used 50µg and 100µg misoprostol vaginally and in 50µg-group Bishop score was 2-5 in 8 (26.7%) cases and 4-5 in 22 (73.3%) cases. In 100µg-group Bishop score was 2-3 in 10 (33.33%) and 4-5 in 20 (66.67%) cases.[7] Similar study was done by Zhang et al based on FIGO guideline for induction of labour and found that the incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery within 24 h was higher in the misoprostol group than in the placebo (64.2% vs. 22.5%, relative risk [RR]: 2.9, 95% confidence interval [CI]: 1.4–6.0).[8] Shakya et al compared safety and efficacy of misoprostol and dinoprostone as cervical ripening agent in 66 women. Patients with Bishop score of 4 or less were randomly assigned to receive misoprostol tablets (n=35, 50**µg** intravaginally) or dinoprostone gel (n=31, 0.5 mg intracervically) at 6 hourly intervals. In the group who received vaginal misoprostol, mean initial bishop score was 3.00±0.90, and bishop score after 12 hours was 6.38±1.9.[9] These findings were similar to our study.

The success of the misoprostol in cervical ripening is taken as the successful vaginal delivery. In this study 54 women were enrolled and 50 (92.6%) of cases had vaginal delivery and 4 (7.4%) had operative delivery. For fetal demise, success of termination was 90.9% at 13-17 weeks and 100% at 18-26 weeks in study done by Shrestha et al.[10] Similar success rate was found in the study by Das et al including 60 women. Among 60 patients 30 received 50**µg** of misoprostol 6 hourly and 30 patients received 100**µg** of misoprostol 8 hourly per vaginally. All were delivered vaginally in both groups.[7] That would make 100% for the 100**µg** group like in our study. Similar findings were noted in a review article by Goldberg et al which stated that in various studies the usual regimen for induction of labour in the second trimester was 200µg of misoprostol given vaginally every 12 hours. With this regimen, the rate of successful abortion (delivery of the fetus within 48 hours) ranged from 71% to 100%. Increasing the frequency of misoprostol administration was

expected to increase efficacy, but in one randomized study of 100 women, 200µg of misoprostol given vaginally every 6 hours was no more effective than the same dose given every 12 hours. Administration of 400µg of vaginal misoprostol every 3 hours (for a maximum of five doses in 24 hours) resulted in complete abortion within 48 hours in 91 percent of women undergoing induction of labour in the second trimester. Vaginal doses of 200µg, 400µg, and 600µg given every 12 hours to women during the second trimester resulted in abortions in 71%, 82%, and 96%, respectively.[11] However, study done by Zhang et al showed incidence of Cesarean Section deliveries 68 (n) (39.3%) compared to placebo, 24 (49.0%), relative risk RR being 0.8 (0.4–1.5).[8] This finding differs from our study. In their study, induction of labour was done in cases with live fetus, unlike ours where the cases had dead-fetus and fetal distress is a know side effect of misoprostol due to uterine hyperstimulation,[11] leading to higher rate of Cesarean Section in their study. In a study by Kwon et al using 50µg of vaginal misoprostol 6 hourly for induction of labour at term, among 82 cases 5 cases had Cesarean Section which were for non-reassuring CTG and non were for failed induction of labour.[12] In our study we had one case of failed induction of labour among 54 cases (1.9%). The difference between that study and our study in terms of rate of failed induction of labour can be due to the dose of misoprostol as we had used 25µg at term. Abediasl et al allocated 40 women with IUFD at 15–24weeks to receive 200µg vaginal misoprostol 12 hourly and induction was failed in 2 cases amongst 40 cases (95% success rate),[13] In our study 16 (29.6%) women were in gestational age group of 13-26 and they had received 200µg of vaginal misoprostol 6 hourly and no case had failed induction of labour suggesting high success rate (100%). However our study had smaller number of cases compared to their study, which decreases the statistical power of our study. Rahimi-Sharbaf et al also showed similar high success rate (96.9%) in their study.[14]

In our study the mean duration of termination, i.e. time from insertion of 1st dose of vaginal misoprostol to delivery in hours was 19.83 ± 13.05 hours. Second trimester was further divided into two groups of 13-26 weeks and 27-28 weeks. In 13-26 weeks (200µg misoprostol) the mean duration of termination was 20.60 ± 15.26 hours and number of cases was 15. In 27-28 weeks (100µg of misoprostol) there were 4 cases and mean duration of termination for that group was 28.50 ± 10.66 hours. There were 31 cases beyond 28 weeks (25µg of misoprostol) and the mean duration of termination in that group was 21.35±13.71 hours. Fletcher et al had similar findings in their study of using 100µg of misoprostol, where the mean duration of insertion to delivery was 21.8 hours. However, the mean gestational age in their study was 38.8 ± 2.8weeks and our study was 30.8 ± 6.7weeks.[3]

In a study by Shrestha et al, median time from induction to delivery for fetal demise was 18 hours for 13-17 weeks and 24 hours at 18-26 weeks respectively. For fetal demise, gestational age of 13-17 weeks received 200µg every 6 hourly to a maximum of 4 doses, and 18-26 weeks dose was adjusted to 100µg.[10]

In study by Shakya et al mean induction to delivery time was 17.99 hours,[9] which is lower compared to our study. The difference is probably because they have used 50µg every 6 hourly in cases beyond 38 weeks, unlike us where we have used 25µg for cases beyond 38WOG. Similar findings were noted in study by Kwon et al using 50µg of misoprostol where the median induction to delivery time was significantly shorter with vaginal misoprostol (15.7 h range 4.3-55.7) in cases at or beyond term.[12] Likewise in the study by Abediasl et al for a gestational age of 15–24 weeks, induction-to-delivery interval was (10.5±5.3 [range 4–27] h) while using 200µg vaginal misoprostol every 12 hourly.[13] Similar findings were noted in study done by Ting et al where the median abortion interval of all 101 patients was 16.5 hours [25-75% interquartile range (IQR) = 9.3-32.7 hours].[15] In study by Lin et al, IUFD of 14–20 weeks or greater than 20 weeks were taken and 200µg of misoprostol was given vaginally every 6 hourly and induction to birth interval was 13.2±7.5 hours.[16]

Side effect of misoprostol was not seen in our study. Abdominal pain was not taken as side effect in our study, as it is one of the sign of onset of labour. Minor side effects like nausea, vomiting, diarrhoea, pyrexia was noted in studies by Shakya et al,[9] Shrestha et al,[10] Abediasl et al[13] and Naz et al.[17]

CONCLUSION

This study concludes that vaginal misoprostol according to FIGO guideline 2017 is safe and effective for preinduction cervical ripening in second and third trimester intrauterine fetal demise leading to successful vaginal delivery, in majority of cases.

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