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CLINICAL ARTICLE

Factors associated with delayed onset of active labor following vaginal misoprostol administration among women at Mbarara Regional Referral Hospital, Uganda

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KEYWORDS

Labor; Misoprostol; Onset; Vaginal

SYNOPSIS

Nulliparity, gestational age less than 37weeks, are associated with delayed onset of active labor following labor induction with vaginal misoprostol.

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ABSTRACT

Objective: To determine the factors associated with delayed onset of active labor following labor induction with vaginal misoprostol.

Methods: We conducted a prospective cohort study over 6 months at a tertiary hospital in Uganda. We enrolled mothers with gestational age ≥28 weeks, who were undergoing labor induction with 50 micrograms of vaginal misoprostol, administered every 6 hours with a maximum of 4 doses and followed them up until onset of active labor. Labor onset was

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considered delayed if it occurred later than 12 hours after the first dose. Bivariate and multivariate analysis was done to determine factors associated with delayed onset of active labor.

Results: Of the 88 mothers enrolled, 22.7% (n=20) had delayed onset of active labor. Nulliparity (aRR: 2.34, 95% CI:1.17-4.68) and gestational less than 37 weeks (aRR: 3.79, 95% CI:1.40-10.23) were associated with delayed onset of active labor following vaginal misoprostol administration while higher BMI (aRR: 0.38, 95% CI:0.18- 0.79) decreased the risk.

Conclusion: Delayed onset of active labor following labor induction remains an important obstetric care challenge. Mothers undergoing labor induction should have their BMI documented while nulliparous and mothers at gestational age <37 weeks should have labor monitored for a longer duration following labor induction.

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1 INTRODUCTION

Induction of labor (IOL) refers to techniques for stimulating uterine contractions to accomplish delivery of the feto-placental unit prior to the onset of spontaneous labor [1]. The goal of labor induction is to stimulate the uterus into active labor and ultimately achieve vaginal delivery. Labor induction should generally be performed when there is a clear medical indication and the expected benefits outweigh its potential harms. Indications for induction of labor among others include gestational age of 41 completed weeks or more, pre-labor rupture of amniotic membranes, hypertensive disorders, maternal medical complications, fetal death, fetal growth restriction, chorioamnionitis, and vaginal bleeding [2].

Although methods for induction of labor include mechanical and pharmacologic approaches, the latter are more desirable. Prostaglandins remain the single most effective means of achieving cervical ripening and inducing labor, providing good clinical effectiveness and patient satisfaction. Compared to other prostaglandins, misoprostol, a synthetic prostaglandin E_1 is preferred because it is stable at room temperature, relatively inexpensive and can be given via several routes namely oral, vaginal, sublingual, and buccal, making it an ideal agent for induction of labor, particularly in settings where resources are limited [3-5].Vaginal misoprostol has been recommended by the World Health Organization as one of the effective methods for induction of labor [2].

Although labor induction targets onset of active labor, some women fail to achieve active labor and vaginal delivery. Currently, there is limited data from resource limited settings to understand how frequently this occurs and even more importantly, the predictors of this failure. Therefore, the aim of this study was to determine the frequency and factors associated with delayed onset of labor following labor induction at Mbarara Regional Referral Hospital.

2 MATERIALS AND METHODS

This was a prospective cohort study conducted from October 2017 to March 2018 at Mbarara Regional Referral Hospital, a public hospital that serves as the major referral site

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for the south western region of Uganda with a catchment population of over 5 million. Annually 12,000 deliveries are conducted at the hospital, and 4.2% of them follow induction of labor.

We enrolled all pregnant mothers at ≥ 28 weeks admitted on the maternity ward who were undergoing labor induction with vaginal misoprostol. According to the MRRH institutional protocol for labor induction, a dose of 50micrograms of vaginal misoprostol (misoclear brand manufactured by ACME formulation private limited, Nalagarh, Himachal, Pradesh), was administered six hourly until onset of active labor up to a maximum of 4 doses. This is partly because the available 200microgram misoprostol tablet can easily be divided into 4 parts of 50micrograms each as opposed to 8 parts of 25micrograms. The participants were reviewed every 2 hours until the onset of labor to ascertain study outcomes. Women who declined to consent to the study were excluded.

We assumed a 95% confidence interval and that nulliparous mothers would have a 1.5-fold increase in the risk of having a delayed onset of labor. A sample size of 88 mothers was therefore sufficient to detect this relative risk with a power of 80%.

Data were collected using an interviewer administered questionnaire and from patient examination findings. The dependent variable was time to onset of active labor. Onset of active labor was defined as having adequate uterine contractions and a cervical dilatation of 4 cm or more. Delayed onset of active labor was defined as failure to achieve active labor after 12 hours following initiation of labor induction.

The other covariates of interest included socio-demographic characteristics, past medical history and obstetric factors. This information was obtained using an interviewer administered questionnaire and clinical information obtained from the participant's medical forms at the time of enrollment. Socio-demographic data included maternal age, education level, employment, district of residence, residence type and body mass index (BMI). The weight and height of the participants were measured at enrollment into the study and the BMI (weight in kilograms divided by height in meters squared) was calculated. The pre-pregnancy BMI was not available.

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Medical history included information being on antihypertensive treatment. Obstetric data collected included parity, gestational age, number of antenatal care visits attended, use of herbs for labor initiation, membrane status (ruptured or intact), bishop score and intrauterine fetal status (dead or alive).

The data were entered in Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and exported to Stata version 13 for analysis (StataCorp LLP, College Station, TX, USA). The participant baseline socio-demographic, medical and obstetric factors were described using means and medians for continuous variables and proportions for categorical variables. The time to onset of active labor was calculated as the time interval between administration of vaginal misoprostol and onset of active labor for each mother.

The proportion of mothers with delayed onset of active labor was calculated as number of mothers who experienced delayed onset of active labor out of all the mothers enrolled in the study.

The factors associated with delayed onset of active labor were established using risk ratios in both bivariate and multivariate analysis. Factors found to be significantly associated with delayed onset of active labor at bivariate analysis were further assessed in a multivariate analysis using modified Poisson regression analysis with robust standard errors together with those with biologic plausibility. A significance level of 5% was used with the corresponding 95% confidence interval.

Ethical clearance to conduct this study was obtained from the Mbarara University of Science and Technology Research Ethics Committee (no.06/08-17) and Uganda National Council of Science and Technology (no. HS2420). Informed consent was obtained from all the study participants.

3 RESULTS

Overall, 96 women underwent induction of labor during the study period. Of these, 4 were excluded because other routes of Misoprostol administration other than the vaginal route, were used. We also excluded 4 women who declined to consent. We therefore enrolled eighty-eight women into the study. The commonest reason for induction of labor was post-

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dated pregnancy (between 41 to 42 weeks of gestation). The other indications included; pre-labor rupture of membranes, pre-eclampsia, intrauterine fetal death and post-term pregnancy (beyond 42weeks of gestation).

Table 1 shows the baseline characteristics of the participants. The mean age was 27 years (SD±5.9) and majority of the participants were aged between 25-34 years. Most of the participants resided in Mbarara district, and had attended at least primary level of education. Most of the participants never used herbs for initiation of labor and were not on antihypertensive medication. The average BMI at the time of delivery was 27.7 kg/m^2 (SD±4.1). Most of the mothers were multiparous, had attended four or more antenatal care visits, with gestational age between 37 and 41 weeks.

The proportion of mothers who experienced delayed onset of active labor was 22.7% (n= 20). The mean time to onset of active labor was 7.7 ± 5.8 hours.

At bivariate analysis, gestational age less than 37 weeks (RR 3.44, 95% CI: 1.53, 7.74), nulliparity (2.14 RR 3.44, 95% CI: 1.00, 4.57) and fetal death (RR 2.27, 95% CI: 1.05, 4.90), were associated with delayed onset of active labor while BMI of 26 or higher (RR 0.34, 95% CI: 0.18, 0.7) reduced the risk. Being on antihypertensive treatment, Bishop score, membrane status (whether ruptured or intact) were included in the multivariate analysis due to their biologic importance despite not being significantly associated with delayed onset of active labor in the bivariate analysis. In an adjusted analysis, the independent factors associated with delayed onset of active labor were nulliparity (aRR 2.34, 95% CI: 1.17, 4.68) and gestational age < 37 weeks (aRR 3.79, 95% CI: 1.40, 10.20). BMI of 26 or higher reduced the risk of having delayed onset of active labor (aRR 0.38, 95% CI: 0.18, 0.79) while bishop score <7 (aRR 2.25, 95% CI: 0.59, 8.68) was not statistically significant as shown in table 2.

4 DISCUSSION

In our cohort of 88 women at a tertiary hospital in Mbarara, southwestern Uganda, 22.7% (n=20) of the mothers had delayed onset of active labor following administration of vaginal misoprostol for labor induction. Being nulliparous, and having gestational age < 37weeks were significantly associated with delayed onset of active labor following administration of

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vaginal misoprostol. Women with BMI of 26 or higher had a reduced risk of having delayed onset of active labor.

The proportion of mothers with delayed onset of labor in our study is higher than that found in studies done in similar settings in resource limited countries. In a study done by Veena, et al, at a multispecialty teaching hospital in Bangalore, the proportion of mothers who failed to attain active labor within 12 hours of initiating labor induction, was 11.5% [6]. The study however used sublingual misoprostol at an interval of 4 hours, which might explain the difference.

In contrast, a study done in India, 9.62% of the mothers who received a similar dose 50μg of vaginal Misoprostol like in our study failed to get into active labor after 24 hours of administration of the drug. The difference in the proportion could be because delayed onset of active labor was determined at 24 hours while in our study we considered 12 hours [7]. In an even more contrasting study done in China, 52% of the mothers receiving vaginal misoprostol failed to achieve onset of active labor with in 24hours. The participants in this study were nulliparous Chinese women who received 25ug of vaginal misoprostol four hourly with a maximum of 3doses and this possibly explains the difference in the findings [8].

In our study, nulliparous women were 2 times more likely to have delayed onset of active labor compared to their multiparous counterparts. Whether labor is induced or spontaneous, its progression is slower in nulliparous women compared to multiparous women [9-11].

Women with preterm pregnancies (gestational age < 37 weeks) were more likely to have delayed onset of active labor. This is partly because uterine responsiveness to uterotonics like oxytocin and prostaglandins increases at term [12]. In a relatively similar study done in Mulago hospital, Uganda, induction-delivery time, a fair indicator of labor progression, reduced with increasing gestational age [13]. Crane and colleagues noted that most of the women with high gestational age attained active labor after only 4 to 6 hours while their counterparts with lower gestational age took longer [14]. Other researchers have however not found gestational age to affect labor progression [15].

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In this study, mothers with body mass index of 26 and above had a reduced risk of having delayed onset of active labor. Previously, some studies have found increasing BMI to be associated with delayed labor progression [16-18]. These studies however predominantly considered BMI measured before 20weeks of gestation. The participants in these studies also had generally higher BMI compared to those in our study who were generally lean women with an average BMI of 27. Other studies have however found no effect of BMI on labor duration [19].

Our study had some strengths. First, it was conducted in southwestern Uganda, making it one of the few studies to investigate this subject in resource-limited settings. Secondly, we assessed women prospectively and followed them up to ascertain study endpoints.

However, our study had some limitations. The study was confined to one regional referral hospital in Southwestern Uganda and the findings may not be generalizable to all the other regional referral hospitals in Uganda or private hospitals. Misoprostol was only available in the strength of 200 micrograms. It was therefore challenging to break the tablet into exactly equal proportions. We used a surgical blade to ensure that the tablet was divided into 4 equal parts. We also did not use cardiotocography to record uterine contractions and fetal wellbeing, as we did not have access to this equipment. Instead, we used abdominal palpation in short intervals to assess uterine contractions.

5 CONCLUSIONS

In conclusion, nulliparity and gestational age < 37weeks are associated with delayed onset of active labor following labor induction with vaginal misoprostol. This finding suggests that women with these characteristics may need monitoring for a longer duration following initiation of labor induction. For obstetricians and midwives operating in settings where both human and infrastructural resources are limited, this is important guidance in managing these mothers. BMI ≥ 26 is protective from delayed onset of active labor. We recommend that large follow up studies with measurements of pre-pregnancy BMI should be carried out to further evaluate the effect of BMI on the labor-induction process in more resource limited setting such as where our study was conducted.

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AUTHOR CONTRIBUTIONS

RK and GRM conceived the idea. RK and GRM supervised data collection. RK, FB, HL,EA, DM, HML and JN participated in data analysis and interpretation. RK, GRM, HML and FB wrote the first draft. All authors read, revised and approved the final draft of the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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TABLE 1 Baseline demographic characteristics of study participants

Variable	Level	Overall	Delayed onset of labor	
		Overall (n=88,100%)	**Yes (n = 20, 22.7%)**	**No (n=66, 77.3%)**
Maternal age category	18-24	33 (37.5)	14 (42.4)	19 (57.9)
	25-34	42 (47.7)	5 (11.9)	37 (88.1)
	35-42	13 (14.8)	1 (7.7)	12 (92.3)
Education level	None	6 (6.8)	1 (16.7)	5 (83.3)
	Primary	36 (40.9)	10 (27.8)	26 (72.2)
	Secondary	28 (31.8)	8 (28.6)	20 (71.4)
	Tertiary	18 (20.5)	1 (5.6)	17 (94.4)
Employment	Unemployed	48 (54.5)	11 (22.9)	37 (77.1)
	Employed	40 (45.5)	9 (22.5)	31 (77.5)
District of residence	Mbarara	58 (65.9)	9 (15.5)	49 (84.5)
	Others	30 (34.1)	11 (36.7)	19 (63.3)
Residence type	Rural	33 (37.5)	11 (33.3)	22 (66.7)
	Semi-urban	22 (25.0)	7 (31.8)	15 (68.2)
	Urban	33 (37.5)	2 (6.0)	31 (93.9)
Number of antenatal care visits	<4	20 (22.7)	5 (25.0)	15 (75.0)
	4	48 (54.5)	11 (22.9)	37 (77.1)
	>4	20 (22.7)	4 (20.0)	16 (80.0)
Parity	Nulliparous	28 (31.8)	10 (35.7)	18 (64.3)
	Multiparous	60 (68.2)	10 (16.7)	50 (83.3)
Gestational age (weeks)	<37	16 (18.2)	8 (50.0)	8 (50.0)
	37-41	55 (62.5)	8 (14.6)	47 (85.5)
	≥42	17 (19.3)	4 (23.5)	13 (76.5)
Bishop's score	<7	66 (75.0)	18 (27.3)	48 (72.7)
	≥7	22 (25.0)	2 (9.1)	20 (90.9)
Maternal body mass index (kg/m^2)	Normal (18.5- 25.9)	30 (34.1)	12 (40.0)	18 (60.0)
	Overweight (26-29.9)	32 (36.4)	3 (9.4)	29 (90.6)

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	Obese(≥30)	26 (29.5)	5 (19.2)	21 (80.8)
Recent use of local herbs	No	57 (64.8)	11 (19.3)	46 (80.7)
	Yes	9 (29.0)	9 (29.0)	22 (71.0)
Premature rupture of membranes	No	70 (79.5)	17 (24.3)	53 (75.7)
	Yes	18 (20.5)	3 (16.7)	15 (83.3)
Intrauterine fetal status	Alive	74 (84.1)	14 (18.9)	60 (81.1)
	Dead	14 (15.9)	6 (42.9)	8 (57.1)
Being on antihypertensive treatment	No	82 (93.2)	18 (21.9)	64 (78.1)
	Yes	6 (6.8)	2 (33.3)	4 (66.7)

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TABLE 2 Bivariate and multivariate analysis for factors associated with delayed onset of labor

Characteristics	**Crude RR (95% CI)**	**P-value**	**adjusted RR (95% CI)**	**p-value**
Antihypertensive treatment				
Not on treatment	Reference		1	
On treatment	1.84 (0.58, 5.85)	0.299	2.01 (1.13, 1.36)	0.172
BMI				
Normal (18.5 - 25.9)	Reference		1	
Overweight and Obese (≥26)	0.34 (0.16, 0.75)	0.008	0.38 (0.18, 0.79)	0.010
Parity				
Multiparous	Reference		1	
Nulliparous	2.14 (1.00, 4.57)	0.049	2.34 (1.17,4.68)	0.016
Gestational age				
37-41	Reference		1	
<37	3.44 (1.53, 7.74)	0.003	3.79 (1.40, 10.23)	0.009
≥42	1.62 (0.55, 4.74)	0.381	1.19 (0.46, 3.11)	0.717
Membrane status				
Ruptured	Reference		1	
Intact	0.69 (0.22, 2.10)	0.510	0.68 (0.19, 2.36)	0.543
Intrauterine fetal status				
Alive	Reference		1	
Dead	2.27 (1.05,4.90)	0.038	0.75 (0.25, 2.21)	0.596
Bishop score				
≥7	Reference			
<7	3.00 (0.75, 12.01)	0.12	2.25 (0.59,8.68)	0.237

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