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A comparison of two dosing regimens of vaginally administered misoprostol for cervical ripening and induction of labour at term: A randomized controlled trial

Yunus Eze Muhammad*, Hauwa Musa Abdullahi[b], Ibrahim Garba Digol[b], Adewale Ashimi*

Department of Obstetrics and Gynaecology, Federal Medical Centre, Birnin Kudu, Jigawa State, Nigeria
[b]Department of Obstetrics and Gynaecology, Bayero University Kano/Aminu Kano Teaching Hospital Kano, Kano State, Nigeria

Abstract

Background: The use of misoprostol in induction of labour has become established, but there exist wide variations in the dosing regimen.
Objective: The aim of this study was to compare the efficacy and safety of two regimens of intravaginal misoprostol for cervical ripening and labour induction at term.
Method: This prospective randomized clinical trial was conducted on 130 pregnant women at term in Aminu Kano Teaching Hospital, Kano, Nigeria. Those who fulfilled the criteria were randomized into 2 groups to receive intravaginal misoprostol tablets for 24 hours. Study group (A) received 4 hourly 25 µg misoprostol and Control group (B) 6 hourly 50 µg of misoprostol. Student t test, chi-square and Fisher Exact test were used to compare variables. P< 0.05 was considered statistically significant.
Results: Both regimens were effective in cervical ripening and induction of labour with 93.8% and 98.5% achieving vaginal deliveries for 25 µg and 50 µg groups respectively. Oxytocin need was significantly higher (p<0.001) in group A (76.9%) compared to group B (23.1%). The Mean induction-delivery interval in hours was significantly shorter (p< 0.001) in group B (19.31±6.91) compared to group A (25.57±7.25). The percentage of women who delivered within 24 hours of commencement of induction was significantly higher (p= 0.002) in group B. There was no difference in the modes of deliveries in both groups (p =0.074). Tachysystole developed in two and three women in group A and B respectively. There were no significant differences between the two groups in neonates with Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, nor the proportion admitted to NICU. There was no difference in the incidence of adverse maternal effects in each group with p- values > 0.05.
Conclusion: The mean induction-vaginal delivery interval and the number of women who delivered within 24 hours were better in 50µg group than 25µg group with no statistical significant difference in mode of deliveries, maternal and neonatal outcomes.

Keywords: Induction, labour, misoprostol, Kano.

Introduction

Induction of labour (IOL) is an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix after the period of viability by any method for the purpose of vaginal delivery.[1,2] It is a common obstetric intervention, which is usually considered when the risks of continuing pregnancy are outweighed by the risks of terminating it.[3,4] The rate of induction of labour varies by location and institution but appears to be increasing.[2-4] In Nigeria, a rate of 3.6% was reported in Kano[2], 6.6% in Maiduguri[4], and 11.5% in Ogoja.[5] The average rates for Africa, Latin America, United Kingdom and the United States of America are 4.4%, 11.4%, 20.0% and 21.6% respectively.[2-4]

One of the most common indications for labour

Corresponding Author: Dr. Yunus Eze Muhammad

Department of Obstetrics and Gynaecology,
Federal Medical Centre,
Birnin Kudu, Jigawa State, Nigeria.
E-mail: yunuseze@yahoo.com

induction is post-date pregnancy and induction for this reason has been shown to reduce the likelihood of perinatal death.[2,6] Other indications for induction include, pre-eclampsia, premature rupture of membranes especially at term or other situations that require termination of conservative management of high risk pregnancies, potential foetal compromise such as foetal growth restriction, non-reassuring foetal surveillance, maternal medical conditions like diabetes, renal disease, significant pulmonary disease, chronic or gestational hypertension, antiphospholipid syndrome, rhesus isoimmunisation, suspected or proven chorioamnionitis, abruptio placentae, and intrauterine foetal death.[1-6]

The contraindications to induction of labour include contraindications to labour or vaginal delivery. Examples of these include previous myomectomy entering the uterine cavity, previous uterine rupture, foetal transverse lie, placenta praevia, vasa praevia, invasive cervical cancer, active genital herpes, and previous classical or inverted T uterine incision.[1,4,7,8]

Several options are available for labour induction. These include mechanical methods of labour induction, amniotomy, Oxytocin and prostaglandins.

Misoprostol is an analogue of prostaglandin E_1 (PGE_1) which was registered in many countries for the prevention and treatment of peptic ulcer disease particularly those caused by non-steroidal anti-inflammatory drugs.[9-12] Its use for this purpose is contra-indicated for pregnant women as it may cause uterine contraction and miscarriage. Misoprostol's undisputable ability to bring on uterine contractions led to it being the major focus of attention for induction of labour in the recent years.[13]

Approximately half of all women undergoing an induction of labour will have an unfavourable cervix that will require some ripening agent like Misoprostol.[14] Labour induction with an unripe cervix will require more uterine activity to effect cervical dilation, potentially causing a longer labour, more pain and stress for both mother and baby, a higher risk of uterine rupture and an increased odds ratio of delivery by Caesarean section (2.29, 95% CI 1.53 – 3.41).[7] The other advantages of Misoprostol are that it is cheaper, stable at room temperature, readily available and effective with optional routes of administration.[14,15] However its ideal dose, route and frequency of administration are still under investigation.[4,15] The judicious use of misoprostol for both gynaecologic and obstetric indications, in appropriate clinical settings, has been shown to reduce maternal mortality.[12]

Until recently, Misoprostol tablets were available only in 200 µg formulations. Trials examining 50µg and 25 µg doses of Misoprostol have involved cutting tablets or making up suspensions of the drug. Uniform concentration of the active drug could not be guaranteed in individual pieces. This may result in variable amounts of the active drug being delivered leading to variable outcomes. Further research on the use of lower doses of vaginal Misoprostol is needed now that 25µg Misoprostol tablets are commercially available. A systematic review with meta-analysis of five randomized trials concluded that intravaginal misoprostol at doses of 50 µg for cervical ripening and labour induction is more efficacious, but it is unclear whether it is as safe as the 25 µg dose.[16,17]

It has been found that when patients are properly selected, misoprostol is safe and more effective than conventional methods of cervical ripening and labour induction, and it heralds the return of all the conveniences of daylight obstetrics.[18,19] Therefore, it is in order to contribute to finding the optimal dosing regimen resulting in delivery of a healthy baby to a healthy mother and without undue prolongation of hospital stay, this study is undertaken.

Methodology

Study Design: It was a prospective randomized clinical trial of pregnant women admitted in the antenatal ward of Aminu Kano Teaching Hospital, Kano, Nigeria.

Inclusion Criteria: The inclusion criteria were consenting women with singleton term pregnancy, no contraindication to vaginal delivery, intact membranes, cephalic presentation, an unfavourable cervix (Bishop's score <6) and an amniotic fluid Index (AFI) of >5.

Exclusion Criteria: The exclusion criteria were non-consenting women, para 5 and above, women with premature rupture of membranes, preterm pregnancy, multiple pregnancy, severe intrauterine growth restriction (IUGR), non-reassuring cardiotocograph(CTG), macrosomia with estimated

foetal weight ⩾ 4000g, non cephalic presentation, previous uterine scar or history of uterine perforation, allergy to prostaglandin, Bishop's score ⩾ 6, severe oligohydramnios, HIV positive status, or any medical disorder except gestational diabetes mellitus (GDM) controlled on diet with estimated foetal weight <4000g, and mild pregnancy induced hypertension(PIH).

Research Procedure: The principal investigator and trained assistants comprising of resident doctors and midwives in postnatal and labour wards were involved in this study. Approximately 32 pregnant women per month were admitted at term for IOL in our antenatal ward during the study period (April 17, 2016 to September 16, 2016). Thus, the sample size (n) consisting of 130 pregnant women was recruited in 5 months. Women fulfilling the inclusion criteria were randomized into two groups: group A (study group) and group B (control group). Women in both groups had misoprostol inserted in the posterior vaginal fornix without the use of a lubricant by the principal investigator or a resident doctor involved in the research if the Bishop score is less than 6. Misoprostol 25 µg (a tablet of Eprostol® 25), was administered into the posterior vaginal fornix 4 hourly in group A and Misoprostol 50 µg (two tablets of Eprostol® 25), was administered 6 hourly in group B) over 24 hours respectively. Further doses of misoprostol are withheld at the achievement of ripened cervix or onset of labour (one or more palpable uterine contractions in 10 min). Administration of misoprostol also was stopped if there was a need for obstetric intervention. Women in this study were monitored by the research team for uterine contractions, hyperstimulation, nausea, vomiting, diarrhoea, fever, shivering and vaginal bleeding. FHR was monitored every 30 minutes by intermittent foetal auscultation. If labour was established or the Bishop's score was 6 or more, the woman was transferred to the labour ward, and artificial rupture of membranes was performed. If a woman failed to establish labour or the cervix was not favourable enough to permit artificial rupture of the membranes after 24 hours, this was considered failed IOL for this study. She was invariably delivered by caesarean section.

The contractile response to prostaglandins varies from woman to woman and is not easily predictable. In the event of hyperstimulation, attempts would be made to remove the prostaglandin from the vagina and labour monitored on continuous CTG. In the presence of less severe FHR alterations, tocolysis with salbutamol inhalation will be used. However, profound alterations in FHR pattern will require immediate operative delivery.

Management of Labour: The women were managed in labour by the consultant led labour ward team using standard care protocol for any intervention in labour. Labour was managed partographically. Oxytocin infusions were commenced in those patients with satisfactory Bishop's score ⩾ 6 who did not have adequate uterine contractions (defined as the occurrence of 3 to 5 uterine contractions in 10 minutes each lasting 40-60 seconds) after maximum exposure to either dose regimen, or had a spontaneous rupture of membranes without having adequate uterine contractions. Oxytocin infusion was not started until at least 6 hours after the last dose of misoprostol. Oxytocin titration was commenced at 5 miu/min and increased at intervals of 45 minutes to achieve adequate uterine contraction pattern of at least 3 contractions in 10 minutes, each lasting for 40-60 seconds. At active phase of labour, routine intrapartum labour managements were without regard to the dosing regimens. The foetal heart rates were monitored by intermittent auscultation every 30 minutes in the first stage and every 15 minutes in the second stage of labour.

The Primary outcomes were duration to achieve cervical ripening or onset of active labour, the induction-to-delivery interval, need for Oxytocin augmentation, and the rate of vaginal delivery within 24 hours. The secondary outcome measures were occurrence of hyperstimulation, uterine hypertonus, tachysystole, abnormal foetal heart rate, non progression of labour, the rate of failed induction, the rate of caesarean section, maternal adverse effects (nausea/vomiting, diarrhoea, fever, shivering, postpartum haemorrhage, uterine rupture), and neonatal outcomes comprising low Apgar score (< 7 at 1 and 5 minutes), incidence of fresh meconium-stained amniotic fluid, and need for NICU admission.

Adequate uterine contractions in this study are defined as three to five contractions in every ten minutes and each lasting 40 to 60 seconds. Uterine

tachysystole is defined as six or more uterine contractions in 10 minutes without concomitant abnormal FHR pattern. Uterine hyperstimulation syndrome is defined as uterine tachysystole or a hypertonic uterus (single contraction lasting for at least 2 minutes) with the presence of an abnormal FHR pattern prompting intervention. Non-progression of labour is diagnosed when there is no change or minimal change in cervical dilatation between two vaginal examinations during the active phase of labour, or no change or minimal change in descent of the presenting part over one hour during the second stage of labour in the presence of adequate uterine contractions.

Data Collection Techniques: All the recruited participants were fully informed about the nature, scope and the potential risks of the study which was followed by an informed consent. Data were collected at recruitment by the principal investigator and trained assistants. Baseline demographic, obstetric and medical histories, and details of delivery and healthcare received till the time of discharge were recorded for all women in a pro-forma.

Data Management and Statistical Analysis: The data obtained were analyzed using MINITAB

Results

One hundred and thirty pregnant women with obstetric or medical indications for induction of labour at term were recruited during the study period. Table 1 shows the demographic characteristics and indications for induction of labour. There was no significant difference in the mean maternal age (t = -0.12, P = 0.903), mean parity (t = -0.43, P = 0.447), gestational age (t = -0.64, P = 0.525), initial Bishop score (t = -0.63, P = 0.530), and indications for labour (Post date (P = 0.681), PIH (P = 0.815), others (P = 1.000)) in the two groups. Postdate pregnancy was the commonest indication in both groups; 48.5% in the 25µg misoprostol group (group A) and 51.5% in the 50µg misoprostol (group B). The mean Bishop score was 3.02±1.55 in group A and 3.18±1.52 in group B.

Table 2 shows labour outcome in the two groups. The mean number of doses of misoprostol that was used in group A (4.18±1.29), was significantly higher than in group B (2.68±1.02) (t = 7.41, P = 0.001). The need for augmentation with Oxytocin was significantly higher in group A (76.9%) compared to group B (23.1%), (X^2= 14.65, P = < 0.001). The Mean induction-delivery interval (hours) was significantly shorter in group B (19.31±6.91) compared to group A (25.57±7.25), (t = 3.24, P = < 0.001). The percentage of women who delivered within 24 hours of commencement of induction was significantly higher in group B, (X^2 = 8.38, P = 0.004). There was no statistical significant difference in the modes of delivery (SVD (P = 0.208), instrumental delivery (P = 1.000), and

Table 1: Maternal demographic characteristics and indications for induction of labour
m= Mean, SD= Standard deviation

Characteristics	25µg misoprostol (n=65)	50µg misoprostol (n=65)	Statistical analysis Test	p-value
Maternal demographics				
Age in years (m±SD)	26.02±6.04	26.14±5.50	t = 0.12	0.903
Gestational age in weeks (m±SD)	40.65±1.48	40.81±1.38	t = -0.64	0.525
Parity; (m±SD)	1.83±1.64	2.05±1.59	t = -0.43	0.447
Nulliparous, n(%)	23(57.5%)	17(42.5%)	X^2 = 0.90	0.342
Multiparous, n(%)	42(46.7%)	48(53.3%)	X^2 = 0.90	0.342
Bishop score, (m±SD)	3.02±1.55	3.18±1.52	t = -0.63	0.530
Indication for labour induction;				
Post-date	48(48.5%)	51(51.5%)	X^2 = 0.17	0.681
PIH	12(54.5%)	10(45.5%)	X^2 = 0.05	0.815
Others	5(55.6%)	4(44.4%)	Fisher Exact	1.000

Table 2: Labour outcome

Characteristics	25µg misoprostol (n=65)	50µg misoprostol (n=65)	Statistical analysis Test	p-value
Number of doses, (m±SD)	4.18±1.29	2.68±1.02	t = 7.41	< 0.001
Oxytocin augmentation, n(%)	30(76.9%)	9(23.1%)	X^2 = 14.65	< 0.001
Induction-delivery interval, n(%);				
< 12 hours	2(16.7%)	10(83.3%)	X^2 = 4.50	0.034
12 – 24 hours	30(43.5%)	39(56.5%)	X^2 = 1.98	0.160
>24 hours	33(67.3%)	16(32.7%)	X^2 = 8.38	0.004
Mean IDI,(hours)	23.73±9.27	18±7.32	t = 3.24	< 0.001
Mean IALO,(hours)	14.79±5.38	12.15±5.39	t = 3.52	0.007
Mode of delivery n(%);				
SVD	60(48.0%)	64(52.0%)	X^2 = 0.20	0.208
IVD	1(100.0%)	0(0.0%)	Fisher Exact	1.000
Caesarean Section	4(80.0%)	1(20.0%)	Fisher Exact	0.365
Birth weight(kg), m±SD	3.16±0.37	3.10±0.35	t = -1.04	0.301

m= Mean, SD= Standard deviation, IDI= Induction-delivery interval, IALO=Induction-active labour onset, SVD= Spontaneous vaginal delivery, IVD= Instrumental vaginal delivery,

Table 3: Adverse effects

Characteristics	25µg misoprostol (n=65)	50µg misoprostol (n=65)	Statistical analysis Test	p-value
Tachysystole	2(40.0%)	3(60.0%)	Fisher Exact	1.000
Meconium stained liquor	5(41.7%)	7(58.3%)	X^2 = 0.09	0.762
Apgar score<7 at 1min	4(57.1%)	3(42.9%)	Fisher Exact	1.000
Apgar score<7 at 5min	2(67.7%)	1(33.3%)	Fisher Exact	1.000
NICU admission	1(50.0%)	1(50.0%)	Fisher Exact	1.000
Maternal side effect;				
Nausea	2(40.0%)	3(60.0%)	Fisher Exact	1.000
Vomiting	1(33.3%)	2(66.7%)	Fisher Exact	1.000
Shivering	1 (50.0%)	1(50.0%)	Fisher Exact	1.000

caesarean section (P = 0.365)) and mean birth weight (t = -1.04 P = 0.301) in two groups.

Table 3 shows neonatal outcomes and maternal adverse effects in the two groups. The development of tachysystole (P = 1.000), Apgar score < 7 at 1 minutes (P = 1.000) and 5 minutes (P = 1.000), meconium-stained amniotic fluid (P = 0.762), admission to NICU (1.000) and adverse maternal effects (nausea (P = 1.000), vomiting (P = 1.000), shivering (P = 1.000)) did not show significant difference in both groups. One woman had vacuum delivery on account of prolonged second stage with maternal exhaustion in group A. Five had caesarean section due to failed induction; four in group A and one in group B. In group A, the baby was admitted because of feeding problems, while in group B, it was due to early neonatal jaundice. There was no perinatal mortality in either group.

Discussion

In this study, both 25 µg (group A) and 50 µg (group B) of vaginally administered misoprostol were effective in cervical ripening and induction of labour with 93.8% and 98.5% achieving vaginal deliveries for 25 µg and 50 µg respectively. This was similar to 85% and 95% respectively reported by Adeniyi et al.[9] However, the 50µg group was more effective than the 25µg, as the mean induction to active phase of labour and the mean induction-delivery intervals were significantly shorter in the 50µg group.

However, Adeniyi et al and Azubuike et al could not demonstrate a statistically significant difference in the induction-delivery interval between the two groups, although the interval was shorter in 50 µg misoprostol group.[9,20] The difference may be as a result of difference in the formulation of misoprostol dosage; preformed 25µg misoprostol tablets were used in this study compared to quartering of 200µg tablets, which may not assure accurate dosages as used in their studies. This may also explain why the incidence of tachysystole in this study was not statistically different ($p > 0.05$).

Tachysytole as a complication of use of misoprostol for cervical ripening and induction of labour has been a contentious issue in other studies.[20] The incidence rate of 3.8% in this study is lower than 14.7% reported by Gupta HP et al, using four hours dosing interval of vaginally administered 50µg misoprostol, and Oxytocin augmentation 4 hours after the last dose of misoprostol.[17] The lower incidence of abnormal uterine contractility in the form of tachysystole and hypertonus in this study may also be due to strict protocol criteria of 6 hours dosing interval in group B arm, and not commencing Oxytocin augmentation earlier than 6 hours after the last dose of misoprostol when indicated. Studies from different literatures have proven that frequency of administration, rather than dose, could be a significant factor in causing these complications.[6,21,22] Therefore, the six hourly dose interval of administration used in the high dose 50µg Misoprostol group in this study could have accounted for fewer incidences of these complications. It has been noted that the effect of misoprostol administered vaginally still lingers for longer than 6 h after a single dose.[23] Thus, multiple dosing at four hourly intervals with high dose 50µg of Misoprostol may have a synergic effect with resultant serious complications. The dosing intervals and the preformed 25µg tablets used in this study, may have accounted for why there was no incidence of ruptured uterus, despite other studies linking misoprostol use to the high incidence of uterine rupture.[20,24,25]

Oxytocin need as well as women who delivered after 24 hours, were significantly higher among the low dose group, as compared to those in the high dose group in this study. A Cochrane review by Hofmeyr et al also revealed that lower doses were associated with more need for Oxytocin augmentation.[10] There was no significant difference that was noted in the incidence of vaginal delivery, failed induction and caesarean section among the cases in the two groups, showing that both high (50µg) and low (25µg) doses of vaginally administered misoprostol were equally effective in inducing labour. This finding was not consistent with the studies of Girija et al and Meydanli et al.[24,26] Has R et al, reported an increase in caesarean section rate in the 50 µg group.[16]

The overall neonatal outcomes; Apgar score and admission to NICU did not show significant difference in both groups. Sanchez-Ramos et al, in their meta-analysis of five randomized clinical trials, reported comparable neonatal outcomes with the two doses. This was in contrast with findings from Gupta et al, who reported higher incidence of

APGAR score <7 at 1-min and admission to neonatal intensive care unit.[17,27]

Adverse maternal effects that occurred in this study were nausea, vomiting and shivering. There was no statistical significant difference in their incidence in both groups. Gastrointestinal side-effects were consistent with findings from other studies, and were significantly increased with high dose group as compared to low dose group.[17,20] This finding may represent the wide range of response to misoprostol in different women.[9]

Conclusion

In this study, vaginally administered misoprostol is safe and effective in cervical ripening and induction of labour in both groups, however, the 50µg group was more effective than the 25µg, as the mean induction to active phase of labour, and the mean induction- delivery intervals were significantly shorter, and Oxytocin need was significantly lower in the 50µg compared to the 25µg group.

The overall neonatal outcome and adverse maternal effects did not show significant difference in both groups.

Recommendations

1. Both 50µg and 25µg intravaginal misoprostol are recommended for use in induction of labour in Aminu Kano Teaching Hospital.
2. Dosing interval of 6 hours is recommended when using 50µg intravaginal misoprostol, to prevent additive effects on the previous dose of misoprostol, which may be responsible for development of side effects.
3. Preformed 25µg intravaginal misoprostol tablets are recommended for use, in order to prevent quartering of 200µg tablets, which may not assure accurate dosages.
4. Larger multicentre based randomized controlled trials (preferably double-blinded), is needed to validate the efficacy and safety of 50 µg vaginal misoprostol in comparison with 25 µg, using preformed vaginal misoprostol tablets for IOL at term.

Limitation

1. A limitation of this study is the lack of blinding after randomization. The clinicians involved in the study were aware of the allocated treatment.
2. This study had a relatively small sample size to exclude the possibility of important differences.

References:

1. Kwawukume EY, Ekele BA. Induction and Augmentation of Labour. In: Kwawukume EY, Emuveyan EE, Ekele BA, Danso KA (eds). Comprehensive obstetrics in the tropics.2nd edition, Asante and Hitsscher printing press. 2015;19:163-167.
2. Osaheni L L, Azubuike KO, Chukwuemeka AI, Chikezie NO, Leonard OA. Obstetric Outcome and Significance of Labour Induction in a Health Resource Poor Setting Obstetrics and Gynecology International 2014, Article ID 419621, 5 pages http://dx.doi.org. accessed March19,2015.
3. Bukola F, Idi N, M'Mimunya M, Jean-Jose WM, Kidza M, Isilda N et al. Unmet need for induction of labour in Africa: secondary analysis from the 2004–2005 WHO Global Maternal and Perinatal Health Survey (A cross-sectional survey). BMC Public Health 2012;12: 722.
4. Srividya S. Induction of Labour. In: Essentials of Obstetrics.eds. Sabaratnam A, Alokendu C, Kumar p. Jaypee 2nd ed. 2011. p382-392
5. Ahmed ZD, Garba I, Nafi'ah T, Yakasai IA. Misoprostol: An Effective Agent for Cervical Ripening and Labor Induction: A 2-Year Review in a Tertiary Centre. *Open Journal of Obstetrics and Gynecology*, 2015; 5,274-279.
6. Ekele BA, Nnadi DC, Gana MA, Shehu CE, Ahmed Y, Nwobodo EI. Misoprostol use for cervical ripening and induction of labour in a Nigerian teaching hospital, Niger J Clin Pract 2007;10(3):234–237.
7. Jane E. Norman Induction and Augmentation of Labour. In: Edmonds D.K(ed). Dewhurst's Textbook of Obstetrics & Gynaecology, Eighth Edition. pp 2012.
8. Leduc D, Biringer A, Lee L, Dy J. Induction of Labour; SOGC Clinical Practice Guideline. J

Obstet Gynaecol Can 2013;35(9).
9. Adeniyi AA, Odukogbe AA, Olayemi A, Oladokun O, Adeniji AO, Aimakhu CO, et al. Randomization of two dosing regimens of vaginal misoprostol for cervical ripening and labour induction in a low resource setting. Niger J Clin Pract 2014;17:287-91.
10. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database of Systematic Reviews. 2003, Issue 1. Art. No.: CD000941.
11. Boers, K.E, Neonatal morbidity after induction vs expectant monitoring in intrauterine growth restriction at term: a subanalysis of the DIGITAT RCT. Am J Obstet & Gynecol 2012; 206(4): 344-356.
12. Modak, R., Biswas, D.K., Ghosh, A., Pal, A. and Mandal, T.K. Comparative Study of Sublingual and Vaginal Misoprostol in Second Trimester Induced Abortion. OJOG. 2014; 4, 751-756.
13. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database of Systematic Reviews. 2006; 2: Cd001338.
14. Kudagi BI, Sailaja I, Kumar PR, Babu CS. A comparitive study of intravaginal misoprostol with intra cervical dinoprostone gel for induction of labour in pregnancy Asian J Pharm Clin Res. 2013:6(2); 174-178
15. Shetty A, Livingstone I, Acharya S, Rice P, Danielian P, Templeton A. Oral misoprostol (100 microg) versus vaginal misoprostol (25 microg) in term labour induction: a randomized comparison. Acta Obstet Gynecol Scand 2003; 82 (12): 1103-1106.
16. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet 2007;99 Suppl 2:S160-7.
17. D Gupta HP, Singh U, Mehrotra S. Comparative evaluation of 25 μg and 50 μg of intravaginal misoprostol for induction of labor J Obstet Gynecol India. 2010;60(1): 51-54.
18. Wagner M. Misoprostol (cytotec) for labour induction. A cautionary tale. Midwifery today 2003;67: 31-33.
19. Kreft M, Krähenmann F, Roos M, Kurmanavicius J, Zimmermann R, Ochsenbein-Kolble N. Maternal and neonatal outcome of labour induction at term comparing two regimens of misoprostol. J Perinat Med 2014;42:603-9.
20. Azubuike IJ, Bassey G, Okpani A. Comparison of 25 and 50 microgram of misoprostol for induction of labour in nulliparous women with postdate pregnancy in Port Harcourt. Niger J Clin Pract 2015;18:263-7.
21. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. Drug Saf 2002; 25: 665-676.
22. Wing DA, Fassett MJ, Guberman C, Tran S, Parrish A, Guinn G. A comparison of orally administered misoprostol to intravenous oxytocin for labour induction in women with favorable cervical examinations. Am J Obstet Gynecol 2004; 190: 1689-1694.
23. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet 2007;99 Suppl 2:S160-7.
24. Girija S, Attibele PM,Comparison of two dosing regimens of vaginal misoprostol for labour induction:a randomised controlled trial. J Turkish-German Gynecol Assoc 2009; 10: 220-5
25. Abdul MA, Ibrahim UN, Yusuf MD, and Musa H. Efficacy and safety of misoprostol in induction of labour in a Nigerian Tertiary Hospital. W Afr J Med.2007; 26(3): 213–216.
26. Meydanli MM, Çalıkan E, Burak F, Narin MA, Atmaca R. Labour induction post-term with 25 micrograms vs. 50 micrograms of intravaginal misoprostol. Int J Gynecol Obstet 2003; 81: 249-255.
27. Sanchez-Ramos L, Danner CJ, Delke I, Kaunitz AM. The effect of tablet moistening on labour induction with intravaginal misoprostol: a randomized trial. Obstet Gynecol 2002; 99:1080-1084.

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