

A Comparison between Two Different Doses of Vaginal Isosorbide Mononitrate in Pre-Induction Cervical Ripening at Term: A Randomized Controlled Study

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Abstract: Objective: The objective of this current study was to evaluate the effect of the vaginally administered nitric oxide donor-isosorbide mononitrate [ISMN] at two different doses (40 and 60 mg sustained release) on the cervix uteri, the mother and the foetus when used for pre induction cervical ripening at term. **Materials and Methods (Study design):** The study design was randomized controlled type. This study was performed at the labour sector of the Women's health tertiary University center between January 2011 and February 2012. One hundred and fifty nulliparous women (n = 150) with uncomplicated singleton, ≥ 37 completed weeks of gestation cephalic presentation left occipito anterior, requiring cervical ripening prior to labour induction (modified Bishop score (MBS) ≤ 6) were allocated by stratified block randomization to receive either ISMN 40 mg (Mono MAK[®]), ISMN – SR 60 mg (Imdur[®] – Astra Zeneca) or the placebo folic acid 5 mg, vaginally on two occasions, at 16 and 48 hours before scheduled admission for labour induction. Data were analyzed by intent to treat. Student, chi-square, Fisher exact, and Mann-Whitney tests were used where appropriate with $P \leq 0.05$ deemed significant. Those women who wish to participate and who understand the nature of this trial will be asked to complete and sign two copies of the written consent form. Cervical status (MBS), maternal blood pressure, maternal pulse rate, non stress test, and various side effects were examined (3) and (6) hours after administration of the vaginal tablet. **Results:** At the current study, the parity, mean maternal age, gestational age, indications for labour induction, modified Bishop score, pulse rate, systolic and diastolic blood pressure, as well as non-stress test were normal and nearly similar among the three studied groups. Women receiving ISMN 40 mg (group A = 50 women) and those receiving ISMN 60 mg – SR (group B = 50 women) showed significant increase of the mean modified Bishop score 16 and 48 hours after vaginal administration as compared to the folic acid group (group C = 50 women) ($P < 0.001$). Thus, there was a significantly greater proportion of women of groups A and B who were favourable for induction of labour after 48 hours in comparison with the control group C. Regarding the mean increase in pulse rate, there was a significant increase in group A and B three hours after starting the trial and persisted up to six hours compared to the control group C ($P < 0.001$). Headache was a significant side effect of ISMN in groups A and B (72% and 80% respectively) as compared to groups C (0%). No serious maternal or foetal side effects of clinical importance were registered. No significant difference in the clinical effect upon cervical ripening between the two ISMN groups A and B. **Conclusion:** Vaginal ISMN leads to significant effect on cervical ripening assessed using the modified Bishop score. Also vaginal ISMN causes headache as well as clinically insignificant maternal haemodynamic changes.

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1. Introduction

There is an increasing interest in carrying out pre-induction cervical ripening. However, there are concerns about the use of prostaglandins, the agents commonly used in hospital settings, for this indication, because these agents induce uterine contractions that may lead to foetal hypoxia⁽⁴⁾. Former *et al.*, in 1996⁽¹²⁾ demonstrated abnormalities in (9%) of foetal heart rate tracing following prostaglandin's induced cervical ripening at term. Around 20% of pregnant women undergo induction of labour in the U.K.⁽²⁴⁾. In primigravidae, the mean time taken from starting induction the delivery is between 15 and 20 hours, of which up to 12 hours is spent in cervical ripening phase before labour itself starts⁽¹⁸⁾.

An agent that ripened the cervix without stimulating uterine activity would be the ideal cervical ripening one⁽⁴⁾. Cervical ripening agents are routinely

used in women with cervixes that are unfavourable which is often defined as a Bishop score of 6 or less⁽³⁾. Mechanical dilating agents such as Foley's catheter and hygroscopic and osmotic dilators have been associated with decreased caesarean section delivery rates when compared with oxytocin alone⁽⁵⁾.

Placebo-controlled studies of pharmacologic ripening agents such as synthetic analogues of prostaglandins E₁ and prostaglandin E₂ have demonstrated reduction in delivery time^(14 and 15).

Isosorbide mononitrate (ISMN) is a nitric oxide donor and vasodilator used primarily for patients with angina pectoris⁽¹³⁾. The discovery that the expression of inducible nitric oxide synthase isoform in the human cervix increases toward the end of pregnancy, suggested a potential therapeutic role for nitric oxide donors in the cervical ripening process⁽²⁶⁾. However, the pharmacokinetics of ISMN following vaginal

administration are still unknown⁽²⁾. In contrast to prostaglandins, nitric oxide donors inhibit rather stimulate uterine contractions, and promote rather than restrict uterine blood flow. Thus nitric oxide donors such as ISMN appear to be the ideal cervical ripening agent prior to labour induction⁽¹⁰⁾.

The aim of this study was to evaluate the effects on the mother and the foetus when ISMN 40 mg or the sustained release 60 mg was administered vaginally for preinduction cervical ripening.

2. Patients and Methods

This single-blind randomized controlled study in a single clinical setting was conducted between January 2011 and February 2012 at the emergency obstetric unit of the Women's Health University Center, Assiut University, Assiut, Egypt, and Comprised (150) nulliparous women who require pre-induction cervical ripening, with modified Bishop Score (MBS) ≤ 6 , singleton pregnancy, cephalic presentation (left accipito anterior) and ≥ 37 completed weeks of gestation. All women will not be formally recruited to the study unless the decisions to induce labour is made. Those women who wish to participate and who understand the nature of this trial will be asked to complete and sign two copies of the written consent form. Exclusion criteria include history of any uterine surgery, cervical dilatation ≥ 3 cm, contraction frequency of ≥ 3 in 10 minutes, presence of a placenta praevia or low lying placenta and significant maternal disease other than diabetes mellitus or pre-eclamptic toxemia. Also, foetal compromise of sufficient severity that daily foetal monitoring is scheduled, is one of exclusion criteria. The following will be indications for early cessation of treatment, admission in labour, spontaneous rupture of foetal membranes or occurrence of antepartum haemorrhage.

The studied population will be classified into three equal groups (50 women each). Group (A) will receive 40 mg ISMN as one tablet vaginally (MonoMack[®]), group (B) will receive 60 mg ISMN-SR also vaginally (Imdur[®] – Aztra Zeneca) and group (C) will receive one tablet folic acid 5 mg vaginally (Nile-CO) as a placebo (control group), on two settings 16 and 48 hours before starting labour induction.

Randomization into the three groups will be in the ratio of 1: 1: 1 using black randomization method to keep the number of patients in each group approximately the same. Maternal pulse and blood pressure were recorded during the ripening process to assess for the incidence of maternal hypotension or maternal heart rate changes. Mean arterial blood pressures and pulse measurements were recorded every 30 minutes. Hypotension was defined as mean arterial pressure ≤ 65 mmHg, and tachycardia was defined as

pulse rate ≥ 100 /per minute. Women were assessed for the presence of known potential side effects from ISMN by patient interview (6) hours after study initiation.

All participants underwent continuous electronic foetal heart rate monitoring and tocometry. Mode of delivery as well as neonatal outcomes were assessed. Secondary outcomes included uterine tachysystole (5 contractions in 10 minutes with or without foetal heart rate decelerations) and any abnormal foetal heart rate patterns during the ripening process irrespective of uterine contraction pattern.

Data were analyzed by intent to treat, and Student 't', Chi-square, Fisher's exact and Mann-Whitney U tests were used where appropriate with $P \leq 0.05$ deemed statistically significant.

3. Results

This current study comprised (150) primigravidae planned for induction of labour. Data were analyzed for to assess the real affect of ISMN on cervical ripening, 150 cases were subjected to receive either 40 mg ISMN vaginally or 60 mg ISMN-SR vaginally, or one tablet folic acid 5 mg as a placebo. Figure 1 demonstrates the flowchart of women throughout the study.

There was no difference in the incidence of maternal tachycardia or maternal hypotension between the three studied groups within the first 16 hours after starting the trial. Also, side-effects were similar between the three groups with regard to nausea, diarrhea, flushing, palpitation as well as dizziness, 16 hours after initiation of cervical ripening trial. No maternal or foetal side effects of clinical importance were registered. However, headache that required analgesia was reported by 72% and 80% of women of group (A) and group (B) respectively, 16 hours after starting induction of labour.

Proportion with unfavourable cervix (modified Bishop score <6) at 48 hours after starting this trial and the requirement for additional cervical ripening agent was similar in groups (A) and (B), but there was a statistically significant difference in the above parameters in women of group (C) (Table 4).

4. Discussion

Cervical ripening prior to labour induction is a continuous dilemma that requires more studies. Early randomized trials showed that the use of vaginal nitric oxide donors such as ISMN for termination of first trimester pregnancy resulted in less pressure required to dilate the cervix when compared to placebo^(11 & 25). However, subsequent studies failed to show a benefit when comparing nitric oxide donors with prostaglandins or with placebo for the same indication^(7, 16, 17, 22 and 23).

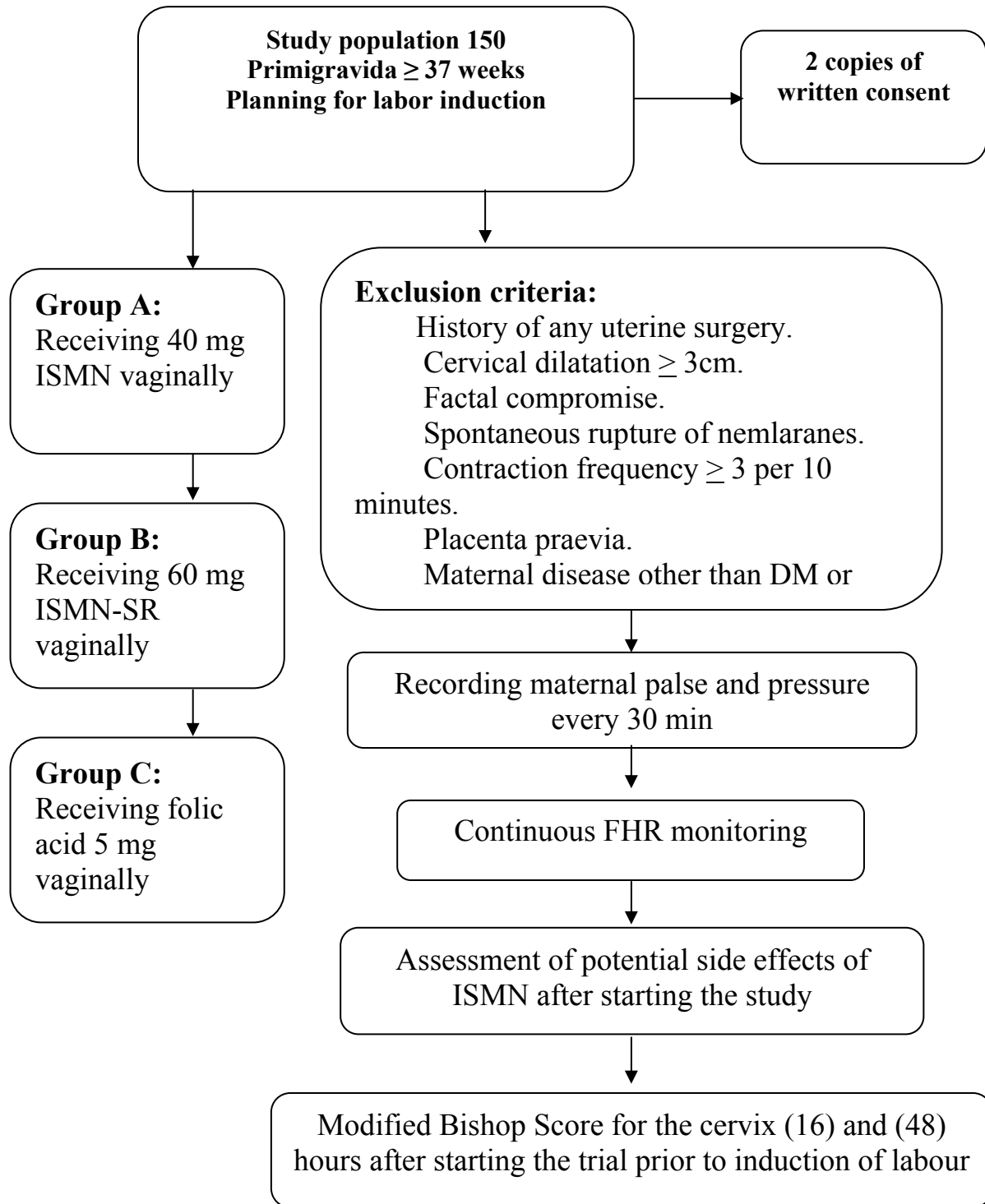


Figure (1): Flowchart of women throughout the study

Table (1): Demographic data of the studied ladies

Data	Group (A) 50 cases 40 mg vaginal/ISMN	Group (B) 50 cases 60mg SRvag. ISMN	Group (C) Folic cid 5 mg Vaginally	Significance
Age (years) Means \pm SD (range)	24.4 \pm 0.8	24.31 \pm 4.9	23.1 \pm 2.8	N.S.
Modified Bishop score before the study	5	4	4	N.S.
Parity	Pgdae	Pgdae	Pgdae	N.S.

Table (2): Modified Bishop Score.

Physical finding	0	1	2	3
Position	Posterior	Mid	Anterior	Anterior
Consistency	Firm	Medium	Soft	Soft
Length (cm)	2	2 – 1	1.5 – 1	\leq 0.5
Dilatation (cm)	0	1 – 2	3 – 4	\geq 5
Foetal head station	- 3	- 2	- 1	+ 1 or lower

Table (3): Incidence of side effects and adverse outcome between the three studied groups within the first 16 hours.

	Group (A)	Group (B)	Group (C)	Significance
1- Maternal tachycardia	2 (4%)	1 (2%)	1 (2%)	N.S.
2- Maternal hypotension	-	1 (2%)	1 (2%)	N.S.
3- Nausea	1 (2%)	1 (2%)	1 (2%)	N.S.
4- Diarrhoea	--	--	--	N.S.
5- Flushing	1 (2%)	1 (2%)	--	N.S.
6- Palpitation & dizziness	--	--	--	N.S.
7- Headache requiring analgesics	36 (72%)	40 (80%)	--	P<0.001

Table (4):

	Group (A)	Group (B)	Group (C)	Significance
Unfavourable cervix at 48 hours after starting the trial	12 cases (24%)	10 cases (20%)	50 cases (100%)	P<0.001
Requirement for additional ripening agent	12 cases (24%)	10 cases (20%)	50 cases	P<0.001

In term gestation, vaginal ISMN for cervical ripening has shown effectiveness as judged by changes in modified Bishop score or cervical distensibility in randomized trials, but with prolonged labour time when compared with vaginal dinoprostone or vaginal misoprostol^(8, 10 and 21).

In this study, we compared two doses of the nitric oxide donor ISMN 40 mg and 60 mg-SR for pre induction cervical ripening compared to a vaginal folic acid 5 mg tablet and it was evident that ISMN per vagina lead to significantly greater cervical ripening after 6 and 48 hours, therefore more women becoming favourable for labour induction.

In contrast to our study, a recent prospective randomized trial⁽⁹⁾ concluded that the addition of vaginal ISMN to oral misoprostol for cervical ripening and labour induction did not reduce, time to vaginal delivery and was associated with a greater incidence of headache.

However our concept was supported by randomized controlled studies which found that the

length of induction to delivery time was reduced significantly with inpatient administration of ISMN combined with vaginal prostaglandins^(1&20).

Our study was a single not double-blind one, in contrast to a similar recent study⁽²⁷⁾, since creation of a placebo tablet that appeared identical to ISMN was problematic, and the alternative of altering the ISMN tablets to appear identical to a placebo would rise the risk of uncertain vaginal absorption.

A recent available data from trials using nitric oxide donors for cervical ripening before labour induction^(4 & 6), concluded that outpatient cervical ripening prior to labour induction with ISMN seems to be an effective, safe and well- tolerated procedure. This was coinciding with the result of our study.

Nearly 75% of women exposed to ISMN developed headaches, that required analgesia in this current study, a comparable finding in other studies using ISMN for cervical ripening at term^(10, 19). To avoid the potential for recall bias when women be aware of the group to which they were randomized and

have been informed of the risk of headache with ISMN before enrollment, we made a single blind study plane. Some recent studies showed statistically significant reductions in maternal blood pressure and increases in maternal pulse with ISMN use at term that were deemed clinically insignificant^(6, 10, 21). Others, showed no significant maternal haemodynamic changes with their combination of a vaginal nitric oxide donor and vaginal prostaglandin⁽²⁰⁾. Our study found no difference in the incidences of maternal tachycardia or hypotension between groups.

An important issue in this study is to evaluate the real effect of the nitric oxide donor, ISMN Upon cervical ripening prior to labour induction. Nevertheless, limitations of this study are many. Both strict inclusion criteria and the lack of follow-up during and after delivery. In our study, despite that we were restricted, our data are also promising for ISMN as a good cervical ripening agent. There is a hard need for more studies on more sample size to make ISMN an established, cheap agent for cervical ripening.

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5. References

- (1) Abdallah M.S., Hussien M., Aboalhasan A., 2011. Intravaginal administration of isosorbide mononitrate and misoprostol for cervical ripening and induction of labour: a randomized controlled trial. *Arch Gynecol. Obstet.*; 284 (1): 25-30.
- (2) Bates C.D., Nicoll A.E., Mullen A.B., Mackenzie F., Thomson A.J., Norman J.E., 2003. Serum profile of isosorbide mononitrate after vaginal administration in third trimester. *BJOG*; 10 (1): 64 – 7.
- (3) Bishop E.H., 1964. Pelvic scoring for elective induction. *Obstet. Gynecol.*; 24: 266-8.
- (4) Bollapragada S.S., Mackenzie F., Norrie J.D., Eddama O., Petrou S., Reid M. *et al.*, 2009. Randomised placebo-controlled trial of outpatient (at home) cervical ripening with isosorbide mononitrate (IMN) prior to induction of labour-clinical trial with analyses of efficacy and acceptability. The IMOP study. *BJOG*; 116: 1185-95.
- (5) Boulven M., Kelly A., Lohse C., Stan C., Irion O., 2001. Mechanical methods for induction of labour. *Cochrane Database of Systematic Reviews*; Issue 4. Art. No.: CD001233.
- (6) Bullarbo M., Orrskog M.E., Andersch B., Granstrom L., Norstrom A., Ekerhovd E., 2007. Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labour induction postterm: a randomized controlled study. *Am. J. Obstet. Gynecol.*; 196 (1) 50 : 1-5.
- (7) Chan C.C., Tang O.S., Ng E.H., Ho P.C., 2005. Intracervical sodium nitroprusside versus vaginal misoprostol in first trimester surgical termination: a randomized double blinded controlled trial: *Human reproduction*; 20: 829 – 33.
- (8) Chanrachakul B., Herabutya Y., Punyavachira P., 2002. Randomized trial of isosorbide mononitrate versus misoprostol for cervical ripening at term. *Int. J. Gynecol. Obstet.*; 78: 139-45.
- (9) Collingham J.P., Fuh K.C., Caughey A.B., Pullen K.M., Lyell D.J., El-Sayed Y.Y., 2010. Oral misoprostol and vaginal isosorbide mononitrate for labour induction: a randomized controlled trial. *Obstet. Gynecol.*; 116 (1): 121-6.
- (10) Ekerhovd E., Bullarbo M., Andersch B., Norström A., 2003. Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term a randomized controlled study. *Am. J. Obstet. Gynecol.*; 189: 1692-7.
- (11) Facchinetti F., Piccinini F., Volpe A., 2000. Chemical ripening of the cervix with intracervical application of sodium nitroprusside: a randomized controlled trial. *Hum. Reprod.*; 15: 224-7.
- (12) Farmer K.C., Schwartz W. J3rd, Rayburn W.F., Turnbull G., 1996. A cost-minimization analysis of intra cervical prostaglandin E₂ for cervical ripening in an outpatient versus inpatient setting. *Clin. Ther.*; 18 (4): 747-56.
- (13) Gunasekara N.S., Noble S., 1999. Isosorbide 5-mononitrate: a review of a sustained-release formulation (Imdur[®]) in stable angina pectoris. *Drugs*; 57: 261 – 77.
- (14) Hofmeyr G.J., Gülmezoglu A.M., 2003. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews*; Issue 1. Art. No.; CD000941.
- (15) Kelly A.J., Kavangh J., Thomas J., 2003. Vaginal prostaglandin (PG E₂ and PG F_{2α}) for induction of labour at term. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD 003101.
- (16) Ledingham M.A., Thomson A.J., Lucan C.B., Greer I.A., Norman J.E., 2001. A comparison of isosorbide mononitrate, misoprostol and combination therapy for first trimester pre-operative cervical ripening: a randomized controlled trial. *BJOG*; 108: 276-80.
- (17) Li C.F., Chan C.W., HO P.C., 2003. A comparison of isosorbide mononitrate and misoprostol cervical ripening before suction evacuation. *Obstet. Gynecol.*; 102: 585 – 8.
- (18) Mckenna D.S., Costa S.W., Samuels P., 1999. Prostaglandin E₂ Cervical ripening without subsequent induction of labour. *Obstet Gynecol.*; 94 (1): 4 – 11.

- (19) Nicol A.E., Mackenzie F., Greer I.A., Norman J., 2001. Vaginal application of the nitric oxide donor isosorbide mononitrate for preinduction cervical ripening: a randomized controlled trial to determine effects on maternal and fetal haemodynamics. *Am. J. Obstet. Gynecol.*; 184: 958 – 64.
- (20) Nunes E.P., Campos A.P., Pedroso S.R. *et al.*, 2006. Intravaginal glyceryl trinitrate and dinoprostone for cervical ripening and induction of labour. *Am. J. Obstet. Gynecol.*; 194: 1022 – 6.
- (21) Osman I., Mackenzie F., Norrie J., Murray H., Greer I. and Norman J., 2006. The "PRIM" study: a randomized comparison of prostaglandin E₂ gel with nitric oxide donor isosorbide mononitrate for cervical ripening before induction of labour at term. *Am. J. Obstet. Gynecol.*; 194: 1012-21.
- (22) Promsontti P., Preechapornprasert D., Chanrachuakul B., 2009. Nitric oxide donors for cervical ripening in first trimester surgical abortion. *Cochrane Database of Systematic Reviews*; Issue 4. Art. No.: CD007444.
- (23) Radulovic N., Norström A. Ekerhovd E., 2007. Outpatient cervical ripening before first-trimester surgical abortion: a comparison between misoprostol and isosorbide mononitrate. *Acta Obstet. Gynecol. Scand*; 86: 344-8.
- (24) Royal college of Obstetrician and Gynecologists: *Induction of Labour*. ROCG2001; London.
- (25) Thomson A.J., Lunan C.B., Cameron A.D., Cameron I.T., Greer I.A., Norman J.E. ,1997. Nitric Oxide donors induce ripening of the human uterine cervix: a randomized controlled trial. *BJOG*; 104: 1054 – 7.
- (26) Tschugguel W., Schneeberger C., Lass H., Stonek F., Zaghulula M.B., Gzerwenka K. *et al.*, 1999. Human cervical ripening is associated with an increase in cervical inducible nitric oxide synthase expression. *Biol. Reprod.*; 60: 1367 – 72.
- (27) Vidanagomage R.S., Goonewardene I.M., 2011. The efficacy of two different doses of vaginal isosorbide mononitrate in pre-induction cervical ripening: a double blind randomized controlled trial. *Ceylon. Med. J.*; 56 (3): 91-100.

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