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Research Article

A Comparative Assessment of Misoprostol and Isosorbide Mononitrate as Cervical Ripening Agents for Surgical Evacuation in First Trimester Missed Miscarriages: A Randomised Controlled Trial

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Abstract:

Background: Cervical ripening is essential to ensure an uneventful surgical evacuation of uterine cavity. Misoprostol is a well-established cervical ripening agent with documented adverse effects. Isosorbide mononitrate (ISMN), a nitric oxide donor appears to emerge as a potential cervical ripening agent with lesser adverse effects.

Methods: A prospective randomized controlled trial was conducted on 120 patients with 60 patients in group – A and 60 in group – B. 400µg Misoprostol and 40mg ISMN were placed per vaginally at zero hour in group A and B respectively. The dose was repeated every three hours (upto a maximum of 4 doses) after a cervical assessment. Cervical ripening was evaluated using Hegars dilators. The number of dilator which could be easily negotiated and time required to easily negotiate a No.10 or larger dilator was assessed. Intraoperative blood loss was assessed. Adverse effects were noted using a symptom questionnaire.

Results: Time required for cervical ripening was significantly lesser (P <0.0001) in group A than in group B (8.63 hrs vs. 10.52hrs). At every assessment women with misoprostol showed higher extent of ripening, 3hrs – 3.4±0.19 vs. 2.6±0.29 (P < 0.0001), 6 hrs - 5.2±0.76 vs. 4.3±0.65 (P < 0.0001), 9 hrs – 8.2±1.56 vs. 7.3±1.48 (P – 0.02), 12 hrs - 11.9±1.89 vs. 9.9±1.48 (P – 0.008). Intraoperative blood loss was significantly higher in women primed with ISMN (89.9±41.41ml vs. 63.4±27.68ml) with a P value of < 0.0001. Adverse effects are seen more with the use of Misoprostol.

Conclusion: Misoprostol appears to cause quick cervical ripening with adverse symptoms whereas ISMN appears to cause slower ripening with lesser adverse effects. Misoprostol appears to be a better drug in emergencies when quick evacuation is required or blood loss has to be minimized. ISMN appears to be a better drug in stable patients with haemodynamic stability.

Key Words: Misoprostol, Isosorbide mono nitrate, cervical ripening, first trimester, surgical evacuation.

INTRODUCTION

Introduction:

Missed miscarriage represents a type of pregnancy loss that mandates surgical evacuation (SE) of the retained products of conception (RPOC) from the uterine cavity. SE-RPOC requires that specific instruments are passed into the uterine cavity through the cervix in order to evacuate the cavity. For this it is required that the cervix of the uterus be favourable to negotiate the instrument/s through it. These changes are collectively referred to as ripening, and essentially include softening of the cervix and opening of the cervical os. Cervical ripening is hence considered as an essential pre-requisite for successful termination of pregnancy and SE-RPOC [1]. Several complications associated with SE-RPOC like uterine perforation and cervical laceration can be minimized by ensuring cervical ripening [2]. This will ensure that the procedure is completed with ease with a better grip on the instrument/s used and controlled manipulation of the instrument within the uterine cavity. As SE-RPOC largely remains a blind procedure, it depends on the obstetrician's skill, perception and appreciation of various tissue consistencies and uterine boundaries. Ensuring proper cervical ripening will ensure easy negotiation which will facilitate the process.

Prostaglandins are well accepted pharmacological agents which cause cervical ripening. These prostaglandin analogues cause both cervical ripening and myometrial contractions. The use of hygroscopic mechanical dilators like laminaria which was more common in the past has decreased over years, as prostaglandin analogues exhibited more effective ripening of the uterine cervix [3]. Misoprostol, a prostaglandin E1 analogue licensed in the UK for cervical ripening in missed miscarriages [4]. The NICE guidelines permit per vaginal and oral route of administration of misoprostol as per the patients comfort and wish. Though misoprostol appears as an ideal cervical ripening agent, it is not devoid of adverse effects. These include, but are not limited to nausea, vomiting, diarrhea, abdominal cramps, vaginal bleed, chills and fever [5].

Nitric oxide (NO) synthetase has been recognized in cervix and NO has been demonstrated as a final mediator of cervical ripening [6]. Several studies have assessed the role of NO in cervical dilatation in animals and humans [7, 8] and have

proved it's cervical ripening potential. Isosorbide mononitrate which is a NO donor is an effective and safe agent for cervical ripening [9, 10]. Vaginal administration of NO donors is not associated with occurrence of any serious adverse effects which may warrant drug withdrawal [11]. ISMN predominantly produces dizziness, headache and palpitation as its side effects among others. These undesirable symptoms appear to be extended pharmacological side effects rather than adverse effects of the drug.

The study was conducted to evaluate the cervical ripening potential of ISMN to Misoprostol. The primary outcomes included the time required to achieve the desired cervical ripening in first trimester SE-RPOC for missed abortions. The rate of cervical ripening was measured in term of the number of Hegars dilator (HD) which could be easily negotiated through the cervix at specific time intervals. Intra operative blood loss and time required to evacuate the uterus was also assessed. Associated adverse effects were observed and compared.

PATIENTS AND METHODS

The study was conducted at the Department of Obstetrics and Gynaecology, ESIC Medical College Hospital, Sanathnagar, Hyderabad, which is a tertiary care teaching hospital with referrals from more than 35 ESIC hospitals and dispensaries. The study was designed as a single blinded, randomized controlled trial and was conducted over a period of one year from April 2016 to March 2017. The study was taken up after approval from the Institutional Ethics Committee and 120 patients were recruited after obtaining written informed consent.

Patients with confirmed ultrasound diagnosis of missed miscarriage (intrauterine gestation sac with no signs of viability) in the first trimester of pregnancy were recruited. These patients were admitted and worked up for surgical evacuation (SE) of retained products of conception (RPOC). Clinical history was obtained and gestational age was calculated by menstrual dates. SE-RPOC was done by removal of RPOC by ovum forceps followed by a gentle curettage using the blunt end of a uterine curette. Both these instruments which had to be negotiated through the cervix were standardised by using instruments provided by the same manufacturer. The width of the ovum forceps at its tip in its largest dimension measured 8.343 mm and the largest dimension of the blunt curette measured 7.783 mm. These measurements were made using standard vernier calipers.

The recruited 120 patients were randomized into Group A and Group B, by using a table of random numbers which were then placed in serially arranged sealed envelopes. A transvaginal scan with a confirmed diagnosis of a non viable gestation with menstrual dates suggestive of gestational age less than 12 weeks were admitted and consecutively worked up. After appropriate investigations and reservation of one unit of cross matched packed cells, the patients were taken up for cervical ripening. One investigator (Dr.MIK) placed the specific medications per vaginally and the other investigator (Dr. AN) assessed parameters for primary outcomes who was unaware of the drug used.

Two tablets of Misoprostol 200 µg (T. Tector 200mcg ©Zee Laboratories Limited) were placed per vaginally in the posterior vaginal fornix at an interval of 3 hours up to a maximum of 4 doses in patients randomized to Group – A and two tablets of Isosorbide mononitrate 20 mg (T.Ismo 20mg © Nicholas Piramal India Ltd.) were placed vaginally in the posterior fornix at an interval of 3 hours up to a maximum of 4 doses in patients randomized to Group – B. Both the tablets were moistened with 4 – 5 drops of saline before placing them per vaginally.

The time of placing the first dose was considered as zero hour consequently Dr.AN assessed cervical changes every 3 hours up to a maximum of 12 hours. Standard Hegar's dilators (HD), procured from the same manufacturer were used to assess cervical dilatation. The HD which could be negotiated easily without any resistance was noted at every assessment. The time required to easily negotiate HD-10 or greater through the cervix was also recorded. Those patients in whom the cervical priming was sufficient to negotiate HD-10 or greater were taken up for SE-RPOC. The size of HD-10 used in the study, measured by vernier was found to be 8.411 mm. The number was standardized to HD-10 as its diameter corresponds closely to the diameter of curette and ovum forceps which need to be negotiated through the cervix.

The procedure was performed by both the investigators with the intra procedural outcomes measured by a nurse who was blinded. Time taken to complete the procedure in minutes was measured from the start of SE-RPOC to signs of complete evacuation. Blood and RPOC were collected in a kidney tray and the RPOC were filtered through multiple layers of gauze and the amount of blood was measured in milliliters. Adverse effects were noted when complained by the patient and specifically all the patients were given a questionnaire about the occurrence of adverse effects and these were noted by the blinded investigator or the blinded nurse.

All mothers with rhesus negative blood type were administered 300 µg of Anti Rh Immunoglobulin (Inj. Plasma Rh_0 300 µg in 2 ml vial ©PlasmaGen Biosciences Pvt. Ltd). Appropriate antibiotic cover was given in accordance with hospital protocols and patients were discharged in stable condition after ensuring complete evacuation by ultrasound.

Data was collected and statistically analysed using Chi Square Test for qualitative data and unpaired t test for quantitative data. Chi square test was performed using online software at www.socscistatistics.com and unpaired t test was performed by using online software at www.graphpad.com.

Inclusion Criteria:

1. Age >18 years and <40 years
2. First Trimester gestation
3. Confirmed non-viable pregnancy (TVS)
4. Confirmed intra uterine gestation
5. Haemodynamic stability at recruitment

6. Normal coagulation profile
7. Normal blood counts, urine analysis, liver and renal functions

Exclusion Criteria:

1. Haemorrhagic disorders
2. Known allergy to the drugs
3. Cardiovascular and / or respiratory morbidity
4. Blood pressure less than 90 systolic and / or 60 diastolic at presentation
5. Patients on Aspirin and / or Heparin
6. Contraindications to the use of ISM – severe anaemia, head injury, severe anaemia, malabsorption syndromes and methaemoglobinaemia
7. Contraindications to the use of Misoprostol – seizure disorders, sickle cell anaemia and glaucoma

Research involving Human Participants

1. All procedures performed on the patient were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1975 Helsinki declaration and its latest amendment in 2000 and other comparable ethical standards.
2. All treatment protocols followed are in accordance with the latest accepted Evidence Based Medicine Norms of the RCOG.
3. Foetal sex was neither detected nor informed in accordance with the PNDT Act 1994.
4. All surgical evacuations were governed by the MTP Act 1971 and its amendments.

RESULTS

After randomization the demographic characteristic (age), obstetric presentations (gravidity, gestational age at presentation) and past obstetric events (parity, previous history of miscarriages) were considered. The same is presented in table -1. None of the differences appear statistically significant, hence the groups are comparable.

Table 1 - Demographic - Obstetric Characteristic

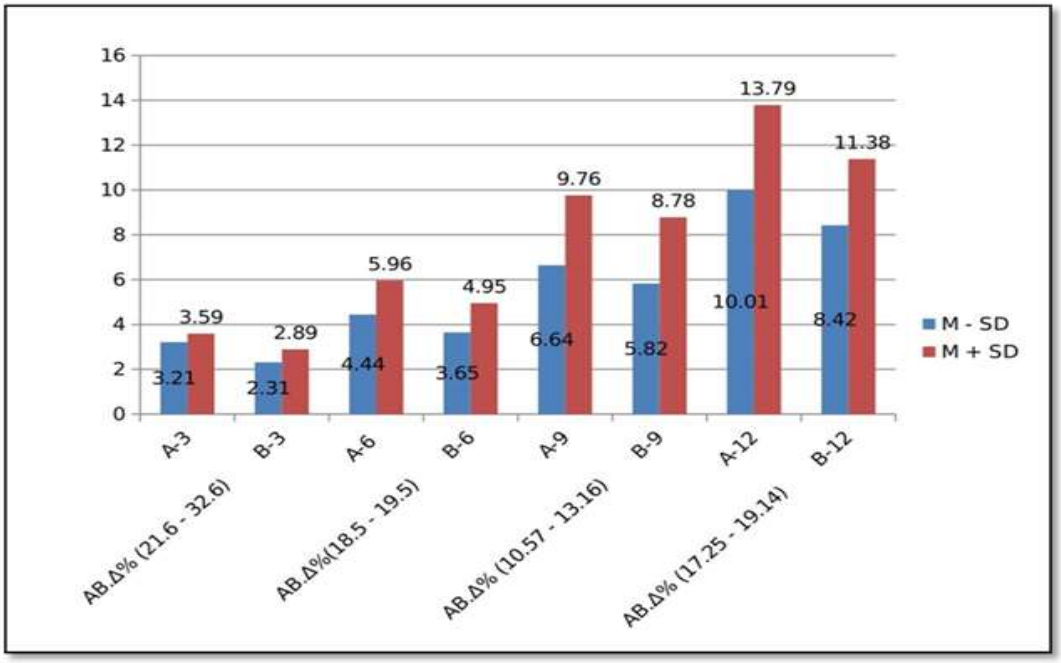
S.No.	Characteristic	Group A Misoprostol 400 µg	Group B ISMN 40mg	P
1.	Age (M ± SD)	24.4±2.37	25.1±1.97	0.08†
2.	Gravidity (M ± SD)	2.13±0.94	2.47±1.17	0.08†
3.	Gestational Age (weeks) (M ± SD)	6.2±1.29	7.1±1.58	0.06†
4.	Parity			
	Primi	18(30)	13(21.67)	0.42‡
	Para 1 – Para 3	33(55)	40(66.67)	
	Grand Multi	9(15)	7(11.67)	
5.	Previous abortions n (%)	13 (21.7)	21 (35)	0.1‡

Table 2 demonstrates the outcomes in terms of cervical ripening in both the groups. All patients were administered the first dose at zero hour and consequently were assessed every three hours. Those patients with cervical dilatation ≥ No.10 HD were not administered further doses. Hence the effects of 1st, 2nd, 3rd and 4th doses were assessed at 3rd, 6th, 9th and 12th hour respectively. It was observed that cervical priming was faster in patients of Group A and was relatively slower in patients who were primed with ISMN. The difference appears to be statistically significant throughout the period of treatment. The time taken for sufficient cervical priming to negotiate the instrument/s (≥ No.10 HD) for SE-RPOC was much lesser in those primed with misoprostol and the difference was found to be statistically significant. The percentage differences (AB.Δ%) in the extent of cervical priming between group A and B is as shown in Figure 1. Consistency in the rate of cervical ripening in group A and group B is compared in table 3. Percentage variance in group B is greater than percentage variance in group A.

Table 2: Assessment of cervical ripening

S.No.	Outcome	Group A	Group B	P
A.	HD (number) passed with ease			
1.	3rd hour (M ± SD) (N_A = 60, N_B = 60)	3.4±0.19	2.6±0.29	< 0.0001
2.	6th hour (M ± SD) (N_A = 42, N_B = 53)	5.2±0.76	4.3±0.65	< 0.0001
3.	9th hour (M ± SD) (N_A = 24, N_B = 40)	8.2±1.56	7.3±1.48	0.02
4.	12th hour (M ± SD) (N_A = 8, N_B = 17)	11.9±1.89	9.9±1.48	0.008
B.	Time taken to easily negotiate ≥ No.10 HD			
1.	Time taken in hours (M ± SD)	8.63±1.62	10.52±2.25	< 0.0001

N_A – Number of patients taken up for further dosing in group A
N_B - Number of patients taken up for further dosing in group B



A-3,6,9,12 : Outcomes at 3rd, 6th, 9th and 12th hour in Group - A

B-3,6,9,12 : Outcomes at 3rd, 6th, 9th and 12th hour in Group – B

AB.Δ% - Percentage difference between Group A and Group B (M+SD to M-SD)

Table 3: Consistency in cervical ripening

S.No.	Group A		б	A.Δ%	Group B		б	B.Δ%
	M – SD	M + SD			M – SD	M + SD		
1st Assessment	3.21	3.59	0.03	11.17	2.31	2.89	0.08	22.3
2nd Assessment	4.44	5.96	0.58	29.23	3.65	4.95	0.42	30.23
3rd Assessment	6.64	9.76	2.43	38.04	5.82	8.78	2.19	40.55
4th Assessment	10.01	13.79	3.57	31.76	17.25	19.14	2.19	29.9
Total percentage variance	110.2				122.98			

б – Variance

A.Δ% - percentage variance in group A at specific assessment

B.Δ% - percentage variance in group B at specific assessment

Intra operative outcomes assessed are tabulated in table 4, blood loss and time taken to complete the procedure was higher in group B patients and these findings were statistically significant. Adverse effects assessed by symptom questionnaire are illustrated in table 5. Total number of adverse effects was higher in Group A (55%) compared to Group B (48.33%). But this difference was not significant. Among specific adverse effects, abdominal pain, diarrhea, fever, nausea and vomiting were reported more in group A and these appeared to be statistically significant. Headache and dizziness appeared to be the only adverse effects occurring in group B.

Table 4: Consistency in cervical ripening

S.No	Characteristic	Group A (M ± SD)	Group B (M ± SD)	P
1.	Blood Loss	63.4±27.68	89.9±41.41	<0.0001
2.	Time taken	7.28±2.15	10.31±2.69	<0.0001

Table 5: Adverse Effects

S.No	Characteristic	Group A	Group B	P
A.	Specific Adverse effects			
1.	Abdominal Pain	24(40)	9(15)	0.002
2.	Diarrhoea	12(20)	2(3.33)	0.004
3.	Dizziness	4(6.67)	23(38.33)	0.0003
4.	Fever	18(30)	4(6.66)	0.0009
5.	Headache	6(10)	14(23.33)	0.05
6.	Nausea	8(13.33)	2(3.33)	0.04
7.	Palpitations	6(10)	12(20)	0.12
8.	Vomitings	4(6.67)	0	0.09
B.	Patient Acceptance			
1.	Adverse Effects	33(55)	29(48.33)	0.46
2.	No Adverse Effects	27(45)	31(51.67)	

DISCUSSION

Missed miscarriage is a rather common obstetric issue which demands immediate attention given the undesirable consequences it potentiates in terms of coagulative disorders. This warrants evacuation of POC to ensure that such morbidities are avoided. Misoprostol or Misoprostol acid or 15-deoxy-16-hydroxy-16-methylprostaglandin E1 is a PG E1 analogue that has established, evidence based role in cervical ripening in first trimester terminations and SE-RPOC. Randomised controlled trials as early as 1997, proved NO donors like ISMN and glyceryl trinitrate to cause effective cervical ripening compared to placebos, when placed vaginally [12].

NO is a naturally occurring substance which mediates several physiological processes including inflammation, immune response, smooth muscle relaxation, vascular haemostasis and neurotransmission [13]. NO donors like ISMN and GTN increase the concentration of NO locally and systemically when applied locally at mucosal surfaces. NO donors have found a place in obstetrics for a variety of therapeutic applications like foetal growth restriction [14], manual removal of placenta [15], and surgical termination of pregnancy or surgical evacuation [12] and for acute uterine relaxation for foetal extraction [16]. Denison et al have reported that NO leads to enhancement of PG production in cervical tissue when tested in vitro [17]. NO is also a smooth muscle relaxant which explains it's cervical dilatation component during ripening by relaxation.

Cervical dilatation and ripening was significantly faster in women treated with misoprostol. At every assessment there was a significantly higher ripening in group A. The time required to negotiate a ≥10 HD through the cervix was also significantly less in group A (8.63±1.62 vs. 10.52±2.25). This time signifies the induction – procedure interval which is clearly much lesser in women treated with misoprostol ($P < 0.0001$). This is in close agreement with initial reports of Thomson et al, who reported PG analogues to be more effective for cervical ripening than NO donors even at lower doses [18]. Our findings are also in line with the results of Nirmala et al who reported a significantly faster ripening with misoprostol in first trimester terminations [19]. Uzma et al also reported a shorter induction ripening interval with the use of misoprostol [20]. Similarly Marie et al [21] and Chan et al [22] also reported a significant reduction in induction – procedure interval with misoprostol in comparion to sodium nitroprusside when used in first trimester termination, but these differences were not statistically significant.

At every assessment there was a higher percentage variance in effectiveness and onset of action, favoring misoprostol. The consistency of cervical dilation or ripening was assessed by variance and percentage variance within each group at every assessment. It was apparent that misoprostol shows less variance and hence more consistency in the rate of cervical ripening when used in first trimester SE-RPOC. Intra operative characteristics in terms of blood loss and time required to complete the procedure were also assessed. Blood loss was significantly less ($P < 0.0001$) in patients treated with misoprostol (63.4ml vs. 89.9ml). This can be explained by the uterotonic effect of misoprostol which closes uterine sinuses and reduces blood loss. Time required to complete the procedure was significantly higher ($P < 0.0001$) in women primed with ISMN (10.31mins vs. 7.28mins). A reduction in procedure time with misoprostol can be explained by its uterine contractibility properties which would create a shearing force between the uterine myometrium and decidual plate at the site of placental attachment. This could separate the POC hence the procedure would only require evacuation of RPOC. Priming with ISMN would also necessitate separation of POC from the uterine wall followed by evacuation. This could be a potential explanation to occurrence of more pre procedural vaginal bleed with the use of misoprostol [21, 22]

Chan et al also reported significant increase in intra procedural blood loss with the use of ISMN [22]. Marie et al also reported comparatively lower blood loss in women primed with misoprostol, but this did not appear statistically significant [21]. Our findings are also in agreement with Chan et al on the relatively lesser procedure time required with misoprostol when compared to ISMN [22].

A total of 55% of patients in group A showed adverse effects symptoms whereas 48.3% reported adverse symptoms in group B. Patients in group B showed significantly higher adverse symptomatology in terms of head ache and dizziness

whereas patients in misoprostol group reported a higher occurrence of abdominal pain, diarrhea, fever, nausea and vomiting. Palpitations occurred more commonly with the use of ISMN, but this was not statistically significant. Overall adverse effects are less with the use of ISMN.Our findings are in line with the results of most of the other authors. The comparative adverse effects reported in several studies as discussed below in table 6.

Table 6: Comparative adverse effects in various studies

S.No	Outcomes	Marie et al [21]		Chan et al [22]		Gabriel et al [24]		Uzma et al [20]	
		A	B	A	B	A	B	A	B
A.	Characteristics								
1.	Number	21	22	100	100	30	30	50	50
2.	Drug	Miso	ISMN	Miso	SNP	Miso	ISDN	Miso	ISMN
3.	Dose	400µg	40mg	400µg	10mg	400µg	80mg	400 µg	80mg
4.	Formulation	Tab	Tab	Gel	Gel	Gel	Gel	Tab	Tab
5.	Route	P/v	P/v	P/v	P/v	I/c	I/c	P/v	P/v
6.	Dosage	Stat	Stat	Stat	Stat	R-3hrs	R-3hrs	R-3hrs	R-3hrs
B.	Adverse Effects								
1.	No Adv effects	52	64	-	-	-	-	-	-
2a.	Abdominal Pain	43	5	48	20	13.3	3.3	12	2
2b.	Pelvic pain	-	-	-	-	60	3.3	-	-
2c.	Backache	-	-	-	-	13.3	13.3	10	10
3.	Diarrhoea	0	0	-	-	-	-	-	-
4.	Dizziness	0	0	-	-	-	-	0	4
5.	Fever	-	-	5	4	-	-	-	-
6.	Headache	0	32	5	12	16.7	60	12	60
7.	Nausea	10	0	13	24	17.2	0	16	0
8.	Palpitations	0	0	4	20	-	-	8	0
9.	Vaginal bleed	10	0	14	6	-	-	-	-
10.	Vomitings	-	-	3	6	10	0	-	-

A – Misoprostol group | B – NO Donor group
Miso – Misoprostol | ISDN – Isosorbide dinitrate
Tab – Tablet | P/v – Per vaginal | I/c – intra cervical | R – Repeat every

CONCLUSION:

NO donors like ISMN are a safe option for use as cervical ripening agent as a pre treatment for SE-RPOC. Though ISMN is a potential cervical ripening agent, Misoprostol appears to be more effective and faster in causing cervical ripening. Misoprostol also appears to cause consistent ripening of cervix. On the other hand ISMN appears to be a slower agent but is associated with much lesser adverse effects when compared to misoprostol. Adverse effects of misoprostol appear to make the process more unpleasant. Moreover the adverse effects of ISMN appear to be extended pharmacological effects and can be avoided by proper intravenous and / or oral hydration.

The definite beneficial effect of misoprostol over ISMN is a reduction of blood loss during procedure. Hence misoprostol appears to be a better agent in cases when quick evacuation is required whereas ISMN appears to be a better agent when there is no urgency for evacuation and patient is haemodynamically stable with sufficient blood reserve.

REFERENCES

[1] - Mohyuddin S, Akhtar S, Shamsi A, Mustafa N, Jabbar T. Comparative study of extra amniotic prostaglandin F2 and increasing intravenous oxytocin infusion for termination of pregnancy. Pak Armed Forces Med J. 2005;55:29-32.

[2] - MacKenzie IZ, Fry A. Prostaglandin E2 pessaries to facilitate first trimester aspiration termination. Br J Obstet Gynaecol 1981;88(10):1033-1037.

[3] - Helm CW, Davies N, Beard RJ. A comparison of gemeprost (cervagem) pessaries and lamicel tents for cervical preparation for abortion by dilatation and suction. Br J Obstet Gynaecol 1988;95:911-915.

[4] - Ectopic pregnancy and miscarriage: diagnosis and initial management. Clinical guideline [CG154] Published date: December 2012. National Institute of Health and Care Excellence.

[5] - Korhonen R, Lahti A, Kankaanranta H, Moilanen E. Nitric oxide production and signaling in inflammation. Curr Drug Targets Inflamm Allergy 2005; 4:471- 479.

[6] - Chwalisz K and Garfield RE. Nitric oxide as the final mediator of cervical ripening. Hum Reprod 1998;13:245–248.

[7] - Qing S, Bier H, Garfield R, Chwalisz K. Local application of a nitric

oxide (NO) donor induces cervical ripening. J Soc Gynecol Invest 1996;3: 462.

[8] - Piccinini F, Fano RA, Volpe A and Facchinetti F. Ripening of the cervix with sodium nitroprusside in nonpregnant women. J Soc Gynecol

Investig 2003;10:438–442.

[9] – Tommiska VM, Nuutila M, Aittomaki K, et al. Nitric oxide metabolites in cervical fluid during pregnancy: further evidence for the role of cervical nitric oxide in cervical ripening. Am J Obstet Gynaecol 2003;188(3):779-785.

[10] - Arteaga-Troncoso G, Villegas-Alvarado A, Belmont-Gomez A, et al. Intracervical application of nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to 1st trimester surgical evacuation of retained products of conception. BJOG 2005;112(12):1615-1619.

[11] - Thomson AJ, Lunan CB, Ledingham M, et al. Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first trimester termination of pregnancy. Lancet 1998;352(9134):1093-1096.

[12] - Thomson AJ, Lunan CB, Cameron AD, Cameron IT, Greer IA and Norman JE. Nitric oxide donors induce ripening of the human uterine cervix:a randomised controlled trial. Br J Obstet Gynaecol 1997;104:1054–1057.

[13] - Korhonen R, Lahti A, Kankaanranta H, et al. Nitric oxide production and signaling in inflammation. Curr Drug Targets Inflamm Allergy 2005;4(4):471-479.

[14] - Mohammed Ismail Khan, Asna Yasmeen, Mulaparthy Swetha. Sildenafil Citrate Improves Ultrasound Doppler Velocimetry Indices in Foetal Growth Restriction – A Randomised Controlled Trial At A Tertiary Care Teaching Hospital in South India. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2017;16(2) :86-92.

[15] – Peng A, Gorman R, Shulman S, et al. Intravenous nitroglycerin for uterine relaxation in the postpartum patient with retained placenta.

Anesthesiology 1989;71:172– 173.

[16] – David M, Halle H, Lichtenegger W, Sinha P, Zimmermann T. Nitroglycerin to facilitate fetal extraction during cesarean delivery.

Obstet Gynecol 1998;91:119 –124.

[17] - Denison FC, Calder AA, Kelly RW. The action of prostaglandinE2 on the human cervix: stimulation of interleukin 8 and inhibition of secretory leukocyte protease inhibitor. Am J Obstet Gynecol 1999;180:614-620.

[18] - Thomson AJ, Lunan CB, Ledingham M, Howat RC, Cameron IT, Greer IA and Norman JE. Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first-trimester termination of pregnancy. Lancet 1998;352:1093–1096.

[19] - Nirmala Duhan, Sonam Gupta, Krishna Dahiya, Daya Sirohiwal, Seema Rohilla. Comparison of isosorbide mononitrate and misoprostol for cervical ripening in termination of pregnancy between 8 and 12 weeks: a randomized controlled trial. Archives of Gynecology and Obstetrics 2011; 283(6):1245–1248

[20] - Uzma Shafique, Farzana Kazmi, Farah Rehana. Vaginal Isosorbide Mononitrate and Misoprostol for Induction of Cervical Ripening Prior to 1st Trimester Surgical Evacuation of Retained Products of Conception. Journal of Rawalpindi Medical College (JRMC); 2010;14(2):101-103

[21] – Marie-Anne Ledingham, Andrew J. Thomson, C. Burnett Lunan, Ian A. Greer, Jane E. Norman. A comparison of isosorbide mononitrate, misoprostol and combination therapy for first trimester pre-operative cervical ripening: a randomised controlled trial. British Journal of Obstetrics and Gynaecology 2001;108:276-280.

[22] - C.C.W.Chan1, O.S.Tang, E.H.Y.Ng, C.F.Li and P.C.Ho. Intracervical sodium nitroprusside versus vaginal misoprostol in first trimester surgical termination of pregnancy: a randomized double-blinded controlled trial. Human Reproduction 2005;20(3): 829–833.

[23] Shanthi Sivakuma , Nalina. S, Rukkayal Fathima , Rekha Radha. Comparison of misoprostol and misoprostol with isosorbide mononitrate in second trimester termination of pregnancy. J. Evid Based Med. Healthc 2016; 3(63): 3424 – 3429.

[24] - Gabriel Arteaga-Troncoso,a Alejandro Villegas-Alvarado,b Aurora Belmont-Gomez, C Francisco J. Martinez-Herrera,b Roberto Villagrana-Zesati,d Fernando Guerra-Infantea. Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomized controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. BJOG 2005;112:1615–1619.