COMPARISON OF MISOPROSTOL AND MISOPROSTOL WITH ISOSORBIDE MONONITRATE IN SECOND TRIMESTER TERMINATION OF PREGNANCY

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ABSTRACT

BACKGROUND
To compare the efficacy and side effect profile of vaginal misoprostol versus misoprostol and isosorbide mononitrate in enhancing cervical ripening in second trimester pregnancy termination.

METHODS
It is a random clinical trial done in 100 patients for mid trimester termination of pregnancy (between 12 and 24 weeks of gestational age). They were divided into two groups:

Group A
Combination of 400 mcg of misoprostol and 40 mg of ISMN placed intravaginally. Repeat doses included combination of 400 mcg of misoprostol and 20 mg of ISMN every 4 hours for maximum 4 doses.

Group B
400 mcg of misoprostol placed intravaginally every 4 hours for maximum 4 doses for termination. In both the above-mentioned groups, T. mifepristone 600 mg was given orally 36-48 hrs. prior to termination.

RESULTS
The mean induction abortion interval was significantly less (7 hrs. 36 mins) in Group A compared with group B (9 hrs. 55 min). There was no statistical significant difference in the amount of mean dose used in both groups. The complete abortion rate within 48 hrs. in Group A was 94%, which shows no statistical significance when compared with Group B complete abortion rates (80%). However, it is interpreted that on adding ISMN, the number of complete abortion rates are higher. There was no failure of abortion in both the groups. The side effects such as pain abdomen and fever were less in Group A (38%) when compared to Group B (78%).

CONCLUSION
Vaginally administered ISMN seems to be safe and effective method in second trimester pregnancy termination. There is a reduction in hospital stay, manpower, economy spent on patient, and a sense of wellbeing from the patient also.

KEYWORDS
Cervical ripening, Isosorbide mononitrate, Misoprostol, Second trimester pregnancy termination.

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INTRODUCTION: Cervical ripening is important prerequisite for the successful termination of pregnancy.[1] Cervical ripening is thus associated with changes in local cytokines, prostaglandins, and metalloproteases as well as in other bioregulators that play role in process of inflammation and in collagen metabolism.[2] Surgical termination of pregnancy is associated with many complications such as uterine perforation, laceration of cervical and incomplete evacuation of the uterus.[3-5]

Prostaglandin analogues induce cervical ripening in two ways by directly acting on the cervix and by stimulating myometrial activity concomitantly. It is associated with several adverse effects such as abdominal pain, gastrointestinal upset, and vaginal bleeding.[6] Isosorbide

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mononitrate is an effective as well as safe agent for cervical ripening.[7,8] Several chemical donors of NO are presently being used in various types of experimental and therapeutic studies and it have been associated with a patient-friendly side-effect profile when administered 3 hrs. before the surgical procedure.[9,10] Nitric oxide is a mediator in many biological processes such as inflammation, immune response, smooth muscle relaxation, vascular homeostasis, and neurotransmission.[11] There are no documented side effects of nitric oxide when administered vaginally.[12]

Side effects of nitric oxide when given through other routes are headache, dizziness, and palpitation. Mifepristone or RU-486 is the antiprogestin approved for use in termination of pregnancy. This drug acts by causing cervical dilatation and also increasing the sensitivity of uterus to exogenous prostaglandins. It thus shortens the induction abortion interval, increase the successful termination of pregnancy, and reduce the total dose of prostaglandins required. Vaginally administered ISMN seems to be safe and effective method in second trimester pregnancy termination. There is a reduction in hospital stay, manpower, economy spent on patient, and a sense of wellbeing from the patient also.[13]

AIM OF THE STUDY: To compare the combination of mifepristone and vaginal misoprostol with isosorbide mononitrate and misoprostol in medical management of second trimester abortions. The comparison involves aspects of efficacy, which are evaluated by means of the difference in success rate of inducing abortion, induction to expulsion interval, rate of manual/surgical removal of the placenta, and the rate of post-abortive haemorrhage. The comparison also includes the safety profile according to the differences in the incidence of side effects in both groups of the study.

MATERIALS AND METHODS: The study was conducted in the labour ward of Institute of Obstetrics and Gynaecology, Egmore (IOG), Chennai, in the period from October 2014-July 2015. The patients included in the study were those with pregnancies from 12 to 20 weeks of gestational age undergoing induced abortion for various medical indications. The assessment of gestational age was based on Last Menstrual Period (LMP) and ultrasound measurement. Following appropriate counseling, informed consent was obtained by explaining about the procedure, associated complications, and need for surgical evacuation as and when necessary. Required laboratory tests were done.

The Inclusion Criteria Were:

1. Patients requesting termination of pregnancy between 12 and 20 weeks in accordance to MTP act.
2. Women greater than 18 years of age.
3. Ultrasonographic confirmation of gestational age and anomalies.
4. Willingness to comply with visit schedule.
5. Willingness to have a surgical abortion if indicated.

Indications for Termination:

1. Anomalous baby.
2. Intrauterine Fetal Demise (IUFD).
3. Termination for social and medical causes.
4. Contraception failure.
5. Severe oligohydramnios.
6. Severe preeclampsia or imminent eclampsia.
7. PPROM.

Exclusion Criteria Were:

1. Pregnancy below 12 weeks and above 20 weeks.
2. Previous uterine scar.
3. Haemorrhagic disorders.
4. Long-term anticoagulant and corticosteroid therapy.
5. Known allergy to mifepristone and misoprostol.
6. Cardiac disorders - Angina, valvular heart disease, arrhythmia, or cardiac failure.
7. Contraindications to mifepristone including chronic systemic corticosteroid use or adrenal disease.

Contraindications to misoprostol including glaucoma, mitral stenosis, sickle cell anaemia, poorly-controlled seizures.

Methodology: Study population consists of 100 pregnant women within gestational age of 12-20 weeks.

Women Were Divided into Two Groups: Group A - Combination of 400 mcg of misoprostol and 40 mg of ISMN placed intravaginally. Repeat doses included combination of 400 mcg of misoprostol and 20 mg ISMN every 4 hours for maximum 4 doses.

Group B - 400 mcg of misoprostol placed intravaginally every 4 hours for maximum 4 doses. In both the above-mentioned groups, T. mifepristone 600 mg was given orally 36-48 hrs. prior to termination.

On Day 1: History regarding menstruation, her last menstrual period, past reproductive history, prior pelvic surgeries, and known uterine anomalies were obtained. Medical history and gynaecological examination were done. Preprocedural counseling in the obstetric department.

Informed consent was obtained. Sonogram to confirm gestational age, placental location, and to confirm anomalies was done.

Investigations: Haemoglobin and blood group and Rh typing-If Rh negative Anti D is given

1. Screening for common sexually transmitted disease - HIV, VDRL.
2. Inj. T.T. and prophylactic antibiotics were given to all patients.

Women received mifepristone 600 mg orally and the time of mifepristone administration was noted unless abortion occurred. Following administration of mifepristone alone, women were asked to return 36 hours later. Mifepristone enters breast milk and can have endocrine effects on the baby and it has half-life of 24-48 hours. Hence, lactating women are advised to avoid breast feeding for 2 days.

On Day 3: Patient admitted in the labour room and treated as inpatient. Preparation of parts done. Vitals checked. General and gynaecological examination done. Combination of T. misoprostol with ISMN or T. misoprostol alone placed in the posterior fornix according to the study group. Reassessment done every 4th hourly, vitals monitored hourly, analgesics, antipyretics, (Temp >100 F), and antiemetics were added if required. Side effects like abdominal pain, fever, nausea, vomiting, diarrhoea, headache, palpitation, hypotension, and tachycardia were noted.

Outcomes Measured:

1. Induction - abortion interval.
2. Total number of dose.
3. Completeness of procedure.
4. Failure of abortions.
5. Onset of side effects.
6. Subjective assessment of the women's comfort in the two groups was also made.

In presenting the results, continuous variables are presented as means with standard deviation and ranges. Difference in continuous variables was analysed by student's t-test for normally distributed data and Mann-Whitney U test for skewed data. The chi-squared test or Fischer's exact test was used to compare categorical data when appropriate P-value <0.05 was considered statistical significant.

OBSERVATION AND RESULTS:

Age Distribution: Age of the patients in this study was between 18 and 36 years in both the group. The mean age was 24.42 years (Standard Deviation - 4.05) in Group A and 25.20 years (Standard Deviation - 4.37) in Group B. The maximum number of patients seeking mid-trimester abortion were in the age group 21-25 years.

Age Group (Years)	Group		Total
	A	B	
Less than 20	11	12	23
21-25	21	14	35
26-30	14	19	33
More than 30	4	5	9

Table 1: Age Distribution

Parity Distribution: Among all the patients studied in Group A, 46% of the patients were primigravida and in Group B 38% of the patients were primigravida. In Group A, 54% of the patients were multigravida and in Group B 62% of the patients were multigravida. Most of the patients seeking mid-trimester abortion in both the group were multigravida. Among multigravid women, most of the patients were second gravida.

Gestational Age	Group		Total
	A	B	
12-16 weeks	28	20	48
16-20 weeks	22	30	52

Table 2: Gestational Age During Termination

Indications	Group		Total
	A	B	
Anomalous Baby	14	16	30
Contraception Failure	3	3	6
Intrauterine Foetal Demise (IUFD)	9	6	15
Medical Indications	4	7	11
Preterm Premature Rupture of Membrane (PPROM)	4	2	6
Severe Oligohydramnios	2	3	5
Severe PIH	2	2	4
Social Causes	12	11	23

Table 3: Indications for Second Trimester Termination of Pregnancy

Number of Doses Required: In Group A, 18% of the patients aborted with one dose whereas in Group B 14% of the patients aborted with one dose. 56% in Group A and 48% in Group B aborted with two doses. In Group A, 76% of the patients aborted with two doses where as in Group B 62% of the patients aborted with two doses.

Number of Doses	Group		TOTAL
	A	B	
One	9	7	16
Two	28	24	52
Three	11	14	25
Four	2	5	7

Table 4: Number of Doses Required

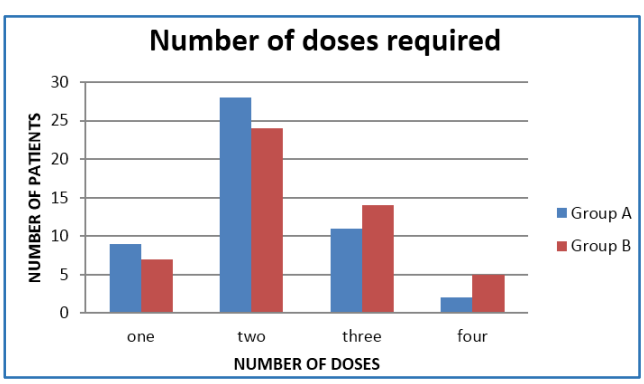

Fig. 1

Group	Mean Dose of Misoprostol Used (µg)	P-Value
A	848	0.097
B	936	

Table 5: Dose of Misoprostol Required

The mean dose of misoprostol used in Group A was less when compared to the mean dose used in group B, but the dose reduction was not statistically significant.

Time Interval	Group		Total	P-Value
	A	B		
0-6 hrs.	18	12	30	0.048
6-12 hrs.	28	22	50	
12-18 hrs.	4	14	18	
18-24 hrs.	0	2	2	

Table 6: Induction Abortion Interval

Induction Abortion Interval: In Group A, the mean duration between induction and abortion was 7 hrs. 36 minutes (Standard Deviation 3 hrs. 11 min.). In Group B, the mean duration between induction and abortion was 9 hrs. 55 minutes (Standard Deviation 4 hrs. 42 min). The P-value was 0.048 and was statistically significant.

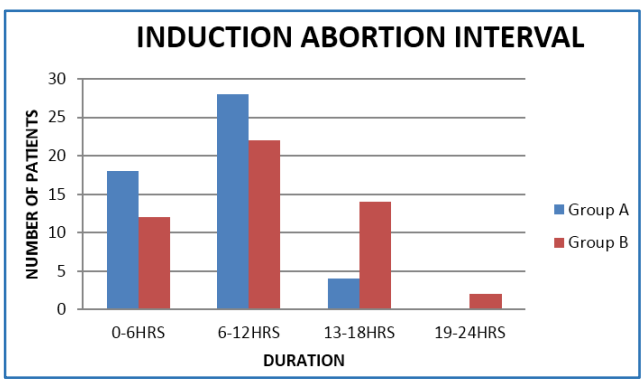

Fig. 2

Side Effects: In this study, the side effects of the drugs used were found in 38% and 78% of the patients in Group A and Group B respectively.

Side Effects	Group A	Group B
Present	19	39
Absent	31	11

Table 7: Side Effects

Comparison of Side Effects: Side effects like pain abdomen and fever were present in more number of patients in Group B when compared to Group A. Major side effects like cervical injury and blood loss were absent in both the groups. The side effect profile is reduced in Group A when compared to Group B, but they are not statistically significant.

Side Effects	Group A	Group B	P-Value
Fever	2	7	0.318
Nausea and Vomiting	0	0	0
Diarrhoea	3	7	0.318
Shivering	1	1	1
Abdominal Pain	19	38	0
Retained Placenta	3	5	0.357
Cervical Injury	0	0	0
Blood Loss	0	0	0

Table 8: Comparison of Side Effects

Side Effects Specific to Isosorbide Mononitrate: Patients in Group A who were induced with additional drug had the following side effects in addition to the above side effects. These side effects occurred in only few of the patients.

Side Effects	Number of Patients
Headache	2
Hypotension	0
Tachycardia	0

Table 9: Side Effects Specific to Isosorbide Mononitrate

Status of Abortion: Among the patients studied, 94% in Group A and 80% in Group B had complete abortion whereas 6% and 16% of women in Group A and Group B respectively had incomplete abortion. There was no failure of abortion in both the group. The number of complete abortion were more in Group A when compared to Group B, but the results were statistically not significant.

Outcome	Group A	Group B	P-Value
Complete Abortion	47	40	
Incomplete Abortion	3	10	0.318
Failure	0	0	

Table 10: Status of Abortion

Time Interval	Parity			
	Group A		Group B	
	Primi	Multi	Primi	Multi
0-6 Hrs.	3	15	5	18
6-12 Hrs.	16	12	11	12
12-18 Hrs.	4	0	2	0
18-24 Hrs.	0	0	1	0

Table 11: Parity and Induction Abortion Interval

Parity and Mean Dose of Misoprostol: As the parity increases, the mean dose of misoprostol used reduces irrespective of the study group.

Mean Dose of Misoprostol in Micrograms	Parity	
	Primi	Multi
Group A	1060	594.5
Group B	1242	686.25

Table 12: Parity and Mean Dose of Misoprostol

DISCUSSION: The current study demonstrates that the combination of ISMN and misoprostol is more effective for second trimester termination of pregnancy than either ISMN or misoprostol alone and results in a shorter induction to abortion interval thus reducing the dosage of drugs used and therefore their side effects.

AGE: The mean age in this study was 24.6±4 standard deviation. The age distribution was maximum amongst the 20 to 25 years and least amongst more than 30 years.

PARITY: Parity distribution shows the maximal distribution among primigravida women 46% in group A and 38% in group B and the rest were multigravida. In this study, all patients aborted without failure. In Group A, 37.25% of primigravida and 74% of multigravida aborted within 12 hours. Multigravid women took significantly less time to abort (P-value-0.044). In Group B, 32% of primigravida and 60% of multigravida aborted within 12 hours. As the parity increases, the mean induction abortion interval decreases in both the groups.

Gestational Age: Gestational age distribution was taken as 12 to 16 weeks (56% and 46%) and 16 to 20 weeks (44% and 60%) in group A and group B respectively. The minimum gestational age in this study was 12 weeks and the maximum was 20 weeks with a mean gestational age of 16.05 weeks ± 2 standard deviation. The mean gestational age was 16.24 weeks (Standard deviation 2.26) and 16.5 weeks (Standard deviation 2.42) in Group A and in Group B respectively. Mean amount of misoprostol used in patients between 12-16 weeks of gestation was more or less equal compared with mean amount used in gestation between 17-20 weeks (618 vs. 664) in group B and shows no statistical significance.

Indications for Termination: The most common indication in the study was anomalous baby (28% and 32%) in group A and B respectively. The indications like severe PIH and severe oligohydramnios were less. Medical indications included severe IUGR, uncontrolled diabetes, maternal medical complications like heart disease, SLE, chronic kidney disease, chronic liver disease. According to Susanne et al in 2010, the most common indications were medical illness, social reasons, and anomalies.

Induction Abortion Interval: In the present study, the time taken for complete abortion in group A ranged from 2.5 hrs. to 15 hrs. In Group A, the mean duration between induction and abortion was 7 hrs. 36 minutes (Standard deviation 3 hrs. 11 min.). In Group B, the mean duration between induction and abortion was 9 hrs. 55 minutes (Standard deviation 4 hrs. 42 min.). The P-value was 0.048 and was statistically significant. In spite of all the other factors remaining the same, the mean induction abortion interval in group A is lesser and is due to the addition of ISMN as an additive drug for termination.

Mean Dose of Misoprostol Used: The mean dose of misoprostol used was lesser in Group A when compared to Group B (848 vs. 936), but, however, it is not statistically significant. The lesser mean dose of misoprostol used is attributed to the use of ISMN as an additive inducing agent.

Mean Number of Dose Used: In Group A, 76% of the patients aborted with two doses where as in Group B 62% of the patients aborted with two doses. Though, it is not statistically significant, the number of doses used for most of the patients in Group A is less when compared to Group B where only 60% patients aborted with two doses.

Success Rate: The success rate of abortion was determined by complete abortion within 48 hours and in our study it was 94% in Group A and 80% in Group B. Also, in group A, almost all the patients aborted within 15 hrs. whereas the time was prolonged in Group B where ISMN was not added. The complete abortion rate in Group A was statistically significant (P value 0.0005). The abortion was considered incomplete if placenta was not expelled within 2 hrs. or if there was presence of retained products of conception, which requires an intervention like check curettage.

The incomplete abortion rate and need for check curettage was higher in group B compared to group A (16 vs. 6%), which is statistically significant. In both the groups, there was no failure of abortion. There are only few studies reporting regimens for women who do not abort within 24 hrs. According to some protocols, if abortion does not occur, mifepristone is given followed by repeated vaginal administration of drugs. Any patient who fails to abort during the second day, we will get a third dose of mifepristone followed by gemeprost 1 mg every 3 hrs.

Side Effects: Side effects like pain abdomen and fever were present in more number of patients in Group B when compared to Group A. Apart from pain abdomen and fever, the incidence of adverse effects was relatively low in both groups. Pain abdomen was seen in 38% in Group A and 76% in Group B. This shows that the addition of ISMN has a definite reduction in the side effect. This is due to the antagonistic effect of ISMN on myometrial contractility without interfering with the abortion process. Side effect specific to ISMN was negligible and reported only in 2 out of 50 patients. This is in accordance with the study, which tells that vaginally ISMN has only local absorption and it enters into systemic circulation only after a maximum of 100 mg. In our study, we found that the addition of ISMN does reduce the incidence of abdominal/pelvic pain or the need to opiate analgesia in the first 24 hours. In contrast, combination therapy reduced significantly the incidence of headache.

The current study demonstrates that vaginally administered ISMN does not affect maternal haemodynamic and hence less degree of side effects. This is in agreement with the findings of Nicolle et al in their randomised controlled trial of IMN in the third trimester. A potential concern regarding the use of NO donors is that their uterine-relaxant effect may promote increased blood loss at the time of delivery. However, the current study reveals that the incidence of postpartum haemorrhage was similar in the study groups. This finding is supported by results of previous studies. The abortion rates and the mean induction abortion interval was significantly more in Group A when compared to Group B. This study correlates well with study by Mousiolis et al who concluded that the combined use of IMN and misoprostol has net benefit in clinical role of ripening of cervix.[14]

CONCLUSION: Vaginally administered ISMN seems to be safe and well tolerated. The mean induction abortion interval was significantly less.

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