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Efficacy of vaginal isosorbide mononitrate with misoprostol versus oral mifepristone and misoprostol in induction of second trimester abortions: An RCT at a tertiary hospital

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Abstract

Objective: To evaluate efficacy of two methods of medical induced abortions in second trimester and to analyse choice of post abortal contraception at a tertiary care centre, in Hassan, Karnataka, India.

Methods: This is a randomised case controlled study between 2017-2019 among pregnant women attending OPD at S.C government teaching hospital, HIMS, Hassan, Karnataka, India and opting for second trimester abortions as per MTP act, India. In the study, among total 158 clients (n=158), Group A(n=79) received oral misoprostol 4hourly for 5 doses after consent and 24hrs prior vaginal 40ugms of Isosorbide mononitrate, and group B(n=79)received 200 milligrams of Mifepristone orally, 24hrs followed by vaginal 400micrograms of misoprostol, and later 4 hourly 400 micrograms oral/vaginally for a total 5doses . The primary outcome indicators such as blood loss, need for transfusions, side effects, complication, need for surgical evacuation, Induction abortion interval and secondary outcome such as choice of post abortal contraception by clients were analysed.

Results: Effectiveness with 5 doses of drugs resulting in Abortion was 78.4% in group T, and 88% in Group C. Side effects were mild, Headache 37%, dizziness and flushing (13%) shivering in group T (23%), were observed in group T, severe patient reported pain was 36% in group C and 23% in group T. Median induction abortion interval in test group was 12hrs and 10.5 hrs in control group=0.048 and statistically significant. 14% women in group T, 10% in Group C needed additional dose of misoprostol. 43% in group T and 35% in group C needed surgical evacuation for removal of placenta and retained products. 2 clients had Rupture/dehiscence of scar uterus was seen in group C in previous scarred uterus, who underwent laparotomy and hysterotomy. 67% of clients for second trimester abortion opted for long Acting reversible contraception (IUCD-41.1%, DMPA injections-30.4%), surgical sterilization 10%, barrier methods 6% and combined oral pills 9% as post abortal contraception.

Conclusion: medical methods are safe, effective in induction of second trimester Abortion including in post caesarian pregnancy, Mifepristone primed medical method of Abortion is more effective and shorter in duration and associated with severe pain. Misoprostol and cervical priming with isosorbide nitrate regime may be used when Mifepristone is not accessible, or in resistant cervix and in scarred uterus as alternate regime.

Keywords: Misoprostol, Mifepristone, median-induction-abortion interval (MIAI), isosorbide mononitrate

1. Introduction

Abortions contribute upto 8% of maternal mortality worldwide¹ that too specifically by unsafe abortions which is a preventable causes of maternal mortality. Abortions in developing countries are often the outcome of lack of awareness in availing early pregnancy- safe abortion services and lack of use of contraception practices.

1.1 Current scenario of abortions in India

Safe induced abortions at hospitals enable women to seek abortion services for unwanted pregnancy, which is an important component of RCH programme in India^[8]. Unsafe abortions contribute to 8% of maternal mortality, and additional 12% burden of increased maternal morbidity^[1]. Termination of unwanted pregnancy is a challenge and is associated with complication. surgical methods have been used earlier with complications and sometimes

necessitates blood transfusions due to incomplete abortion related complications. In India, approximately 2.1 million abortions performed are safe, as a result of comprehensive abortion care services provided by skilled service providers, but the maternal morbidity and mortality are due to unsafe abortions and delayed approach by clients for abortions. Various techniques such as surgical and medical methods for induction of abortions are currently used, among which medical abortions are popular and appear to be safe, and efficient [1-6]. Failure to abort with medical method necessitates search for alternate drugs and methods.

Second trimester Abortions contribute to 10-15% of all induced abortions in the world, among them 1/3 are responsible for major abortion related complications, which is more in late abortions. Expansion of use of medical abortion in second trimester avoids surgical related complications, and is associated with higher incidence of incomplete abortion and long induction-abortion intervals and failed method. Failed medical abortion necessitates use of alternate method for abortion, Resulting in anxiety and impatient behavior of client, prolonged treatment and stay at hospital, with additional financial burden to pregnant women seeking second trimester abortion. Hence there is a need to find alternate regimens, drugs, dosages, and premedications in addition to standard medical abortion drugs. Misoprostol only dosages, Methotrexate with misoprostol combinations, Mifepristone with Misoprostol [7, 8], cervical priming Foleys catheter or with letrozole as pretreatment have been practiced for 2nd trimester induced Abortions with various results as seen in previous studies [9]. Mifepristone is a progesterone antagonist, causes decidual necrosis, and sensitises uterus for contractions. Misoprostol is a prostaglandin E1 analogue that causes uterine contractions, and can be used by oral, sublingual, vaginal, intra cervical routes. Vaginal Misoprostol is associated with slower clearance, lower peak plasma levels, and greater effects on cervix and uterus, sublingual route has rapid absorption and higher peak levels than either vaginal or oral administration and higher gastrointestinal side effects, buccal route has similar effects as vaginal routes. Isosorbide nitrate is a Nitric Oxide donor and causes its effect by NO rearrangement of collagen, with effective pre induction cervical ripening without stimulating uterine contractions [13]. Isosorbide mononitrate has been used in earlier studies for cervical ripening in induction of labour at full term pregnancy [11, 21]. It has been used earlier for cervical ripening before first trimester surgical evaluation [12-19]

Present study is a prospective, randomized, case controlled study between 2017-2019, to compare the efficacy, safety and acceptability of two medical methods in induction of second trimester Abortions at S.C. Government teaching hospital, a tertiary care centre, HIMS, Hassan. This study is conducted to compare efficacy, safety of vaginal isosorbide mononitrate 40ugm followed by vaginal misoprostol 400ugm and repeated 4th hourly versus oral mifepristone 200ugm followed 24 hrs later by 4th hourly vaginal misoprostol-400 u gm. repeated for 5 doses.

2. Materials and Methods

2.1 Methodology-Aim and Objective

Primary objective: To assess

1. The efficacy of above drugs in second trimester induced abortions
2. To assess the safety of both regimens
3. To compare the sideeffects and complications of both regimens
4. To evaluate the need for a second method for completion of abortion

5. Secondary Objective- To assess the willingness for post abortal contraception and contraceptive choice of client.

2.2 Method

This is a randomized, case controlled study among women seeking abortion in second trimester (12-20weeks) of pregnancy. A Institutional review board and Ethical committee approval was taken prior to initiation of study. After history taking and clinical examination and confirmation of pregnancy, basic investigations were conducted to screen and exclude high risk women. An Ultrasound was performed for confirmation of diagnosis, gestational age, to exclude low lying placenta, and abnormality of uterine cavity. Pregnant women selected and recruited for the study are termed as clients. A counselor conducts a counseling session to the couple regarding, selection criteria, methods, and a written informed consent in Medical termination of pregnancy form is obtained by client. The groups are divided into Test (T) and control (C) by Randomized Sampling method- randomization by odd number allocation to Test group (T) as follows. 1, 3, 5, 7, 9, 11, 13, 15, 17,.....T, and the method is selected by single blinding in serially numbered closed envelopes, the total Sample size is n = 158.

2.3 Inclusion criteria

Among women in second trimester of pregnancy (clients attending the out patient department at S.C. Government teaching hospital, HIMS, Hassan), with a singleton intra uterine pregnancy, and needing and willing for termination of pregnancy as per indications under MTP ACT-India, including PPROM with no liquor, lethal fetal anomaly, severe DM and PIH were enrolled in the study.

2.4 Exclusion criteria

Clients in second trimester of pregnancy with medical disorders such as, multifetal gestation, low lying placenta, Renal, liver, thyroid, chronic Adrenal disorders, history of drug allergy or Asthma, cardiovascular, nervous system disorders, uterine anomaly, bleeding diathesis, concurrent use of corticosteroids, inherited porphyria, thrombocytopenia, sepsis were excluded from this study.

Clients with an indication for second trimester Termination of pregnancy as per MTP ACT INDIA, 1971, were recruited for the study based on inclusion and exclusion criteria. Group T (Test) received single dose 20x2 tab vaginal-isosorbide mononitrate followed by oral/vaginal 400 ugm tab misoprostol after 24 hrs, later 4th hourly 400 U gm for a maximum of 5 doses. Group C (control)-received 200 milligrams of mifepristone orally/vaginal, and 24hrs-later followed by vaginal 400micrograms of misoprostol, and later 4th hourly 400 micrograms oral/vaginally (Client preference) for a maximum of 5 doses. Observations were made, regarding-Efficacy as complete abortion in percentages, induction abortion interval-time, need for blood transfusion (Assessed by pre and post test HB levels), failure of method in group is defined as non induction of uterine contractions and expulsion of products within 24 hours and after 5 doses of drugs, assessed by onset of pain /vaginal bleeding and cervical changes or untoward events /complications, Incomplete procedure, retained placenta & surgical concomitant procedures and client Acceptability of procedure by visual assessment of pain score, safety of drug-dosage by incidence of side effects and complications, Concurrent contraception methods accepted by client, comparison of cost involved among groups. The results were analysed by Statistical analysis tool-Ms Excl, SPSS17 software

and the chi-square test $\chi^2=6.7$, difference of $p<0.05$ is considered to be statistically significant difference between test groups.

3. Results and Observation

This study was conducted among 158 clients after evaluating for exclusion criteria and groups were divided into Test (T=79), and Control (C=79) groups including previous one and two post caesarian pregnancy. The observations in both groups such as Median Induction Abortion Interval (MIAI), side effects, retained placenta incidence, distribution of cases, rupture of uterus, Excess Haemorrhage, need for blood transfusion, and choice of post abortal contraception practiced by clients were tabulated.

3.1 Observations-distribution of cases

The distribution of clients in each group is as shown in Table 1 and Fig 1.

Table 1: Distribution of cases

Gest. age in weeks	Group T N=79	Group C N=79
12-16wks	38	33
17-20wks	41	46
Total=158	N=79	N=79

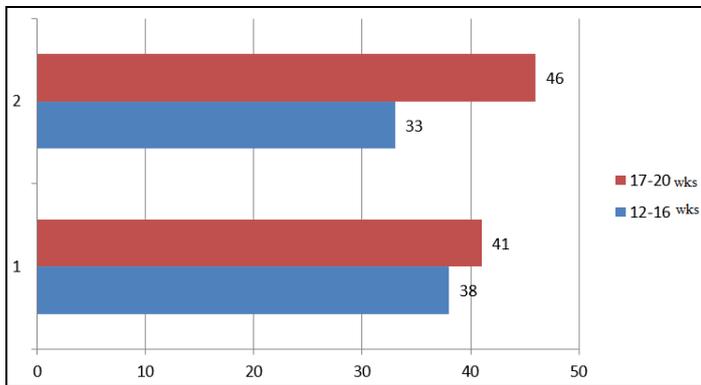


Fig 1: Distribution of cases

3.2 Results-age of mother-distribution of cases

Most of clients were married women in age groups 21-30 years as shown in Table 2 and Fig 2.

Table 2: distribution of cases

Mother's age	Group T N=79	Group C N=79	95% CI
15-20yrs	03	05	3-6
21-25yrs	46	44	40-48
26-30yrs	25	24	22-28
31-35yrs	03	02	02-5
>35yrs	02	04	2-5
Total	79	79	

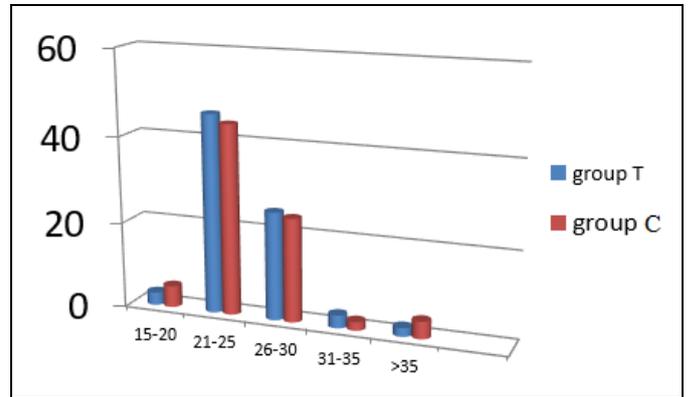


Fig 2: Age distribution of cases

3.3 Observations- Indications for abortion

66% of clients underwent termination of pregnancy for high risk maternal conditions, 71% for lethal fetal anomaly. 66% among clients with high risk pregnancy with severe complications such as diabetes, Eclampsia, PPRM, SLE, on lethal anti psychotic medications etc, women with pregnancy with previous one and two caesarian scar were included in this study.

Table 3: observations- Indications for abortion

Indication	Group T	Group C
fetal anomaly	36	35
Severe medical disorder/high risk	28	38
failed contraception / sterilisation	03	01
social reasons/risk involved to mother and baby	10	11
seropositive status	02	00
previous lscs in both groups	31	18

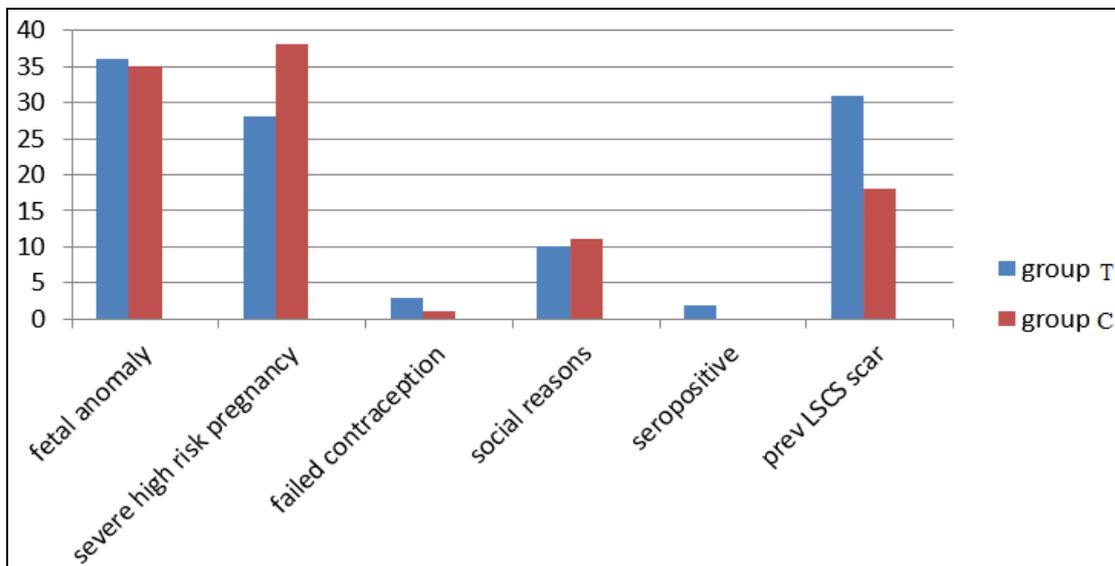


Fig 3: indications for Abortion

3.4 Results

Side effects and complications Complete Abortion was observed in 78.4% in group T, and 88% in Group C. Side effects such as Headache 48%, dizziness, and flushing 16%, chills 10%, were observed in group T and 5%, 32% and 3% in group C. Severe pain as per Wong Bakers visual Scale was observed in 23% in group T and 47% in group C. Analysis of patient reported discomfort based on chi-square test $X^2=6.6$ test, showed

significant difference between two groups ($p=0.014$). Surgical Evacuation and removal of placenta and retained products was needed in 27% of group T and 20% in group C (p value 0.06). 2 clients in group C underwent hysterotomy for Rupture/dehiscence of scar in previous scarred uterus. Blood transfusion was needed after the procedure in 4 women (5%) in group T and 6, (8%) in group C. The observations are as shown in table 4 and fig 4

Table 4: side effects and complications

Side effect/ complication	Group T-n=79	Group T-%	Group C-n=79	Group C-%
vomiting	40	51	32	41
fever and flushing	13	16	25	32
chills	08	10	02	3
Need for blood transfusion	04	5	05	6
Incomplete abortion	21	27	16	20
severe Pain	18	23	37	47
diarrhoea	07	9	10	13
headache	38	48	04	5p(<0.001)
dehiscence	00	00	02	2.5

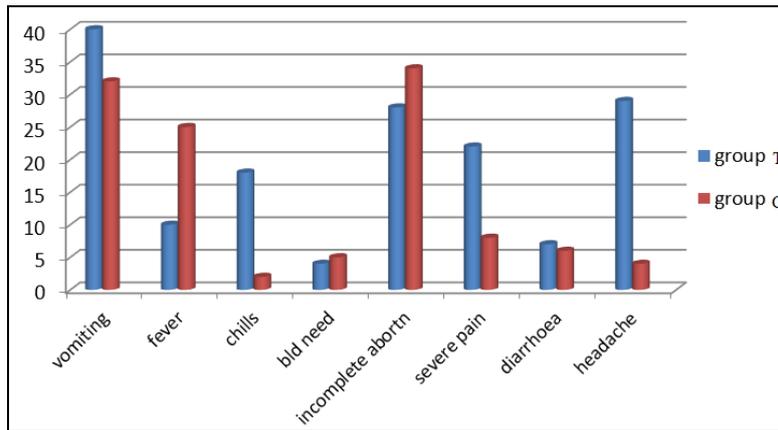


Fig 4: Side Effects

3.7 Induction –abortion interval (I-A-I)

Median induction abortion interval in test group was 12hrs and 10.5 hrs in control group= 0.048 and statistically significant, as

shown in Table 5, fig5. Most in both groups aborted with in 24 hours, and remaining needed additional dosages.

Table 5: Induction –abortion interval

I-A-I in hrs	Group T n=79	Group T%	Group C n=79	Group C%
<8hrs	00	0	10	13
8-11	01	1.3	20	25
12-15	14	18	29	37
16-20	35	44	11	14
21-24	20	25	5	6
>24hrs	9	11	4	5

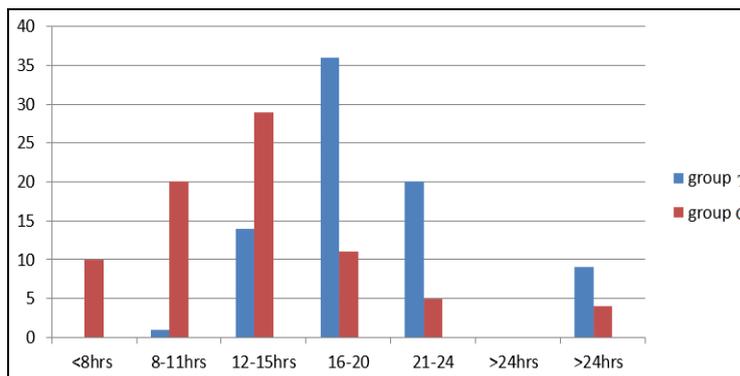


Fig 5: Inducton Abortion Interval

3.8 Results-post abortion contraception accepted

67% of clients undergoing second trimester Abortion opted for long Acting reversible contraception, (IUCD-41.1%, Depot progesterone injections-30.4%), 10%-surgical sterilization, and 6% barrier methods and 9% hormonal combined pills as post abortion contraception. 2 of clients with Previous 2 caesarian delivery and had scar dehiscence/ruture and underwent hysterotomy with concurrent sterilization.

4. Discussion

This study is a Randomized controlled study with study design as shown below, with total number of cases 158 and 79 in each group as shown in clinical trial design fig 10.

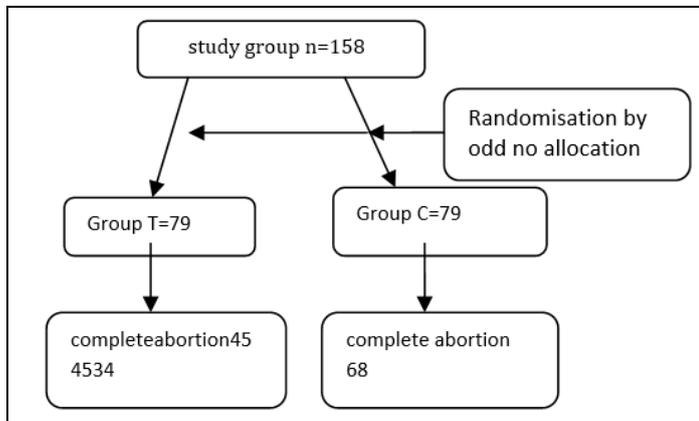


Fig 6: clinical trial design

Various studies and systemic reviews have been reported with different drugs, dosages, routes of administration in combinations and as single drug regimens for termination of second trimester pregnancy [9]. Results are varying. The present study is conducted to assess efficacy, safety of minimal drug, dosage and compared with most used regimen. oi shah Tang, Chung HO MD, in their study observed Mean induction abortion interval of 6hrs with Mifepristone and misoprostol and completion of abortion in <24hrs among 90% [9]. karkia A, *et al.* [7] had a success rate of 90.5% with 5 doses of misoprostol with median IAI of 4-7 hrs, and discussed the conversion to surgical evacuation rate of 6.6% in their study with Mifepristone and repeated misoprostol combination regimen.

Singh v *et al.* [8] reported completion of abortion in 97% in Mifepristone group, and mean IAI 195.8 min compared to control 1318min, and side effects vomiting in 20%, diarrhea in 10%, fever 7%, pain 5%, shivering 10%, and compared with misoprostol group side effects as, 32.5%, 10%, 17.5%, 15%, 7.5% respectively. In present study, Side effects such as Headache 48%, dizziness, and flushing 16%, chills 10%, were observed in group T and 5%, 32% and 3% in group C. Severe pain was observed in 23% in isosorbide mononitrate group in comparison with 47% in misoprostol group. Analysis of patient reported discomfort was higher in Mifepristone group and showed significant difference between two groups ($p=0.014$). Surgical Evacuation and removal of placenta and retained products was needed in 27% of group T and 20% in group C (p value 0.06). patel V [10] *et al* observe Mean IAI of 18.94 vs 24.2 hrs in meoprstone vs misoprostol only group.

Bijeta, Neelam nalini [9], medical method of second trimester abortion with Mifepristone and misoprostol vs misoprostol alone observed most women in Mifepristone group (42) aborted <6hrs compared to misoprostol only group (14) and side effects were more in misoprostol only group. Berghese V *et al.* [10] in his

study with Misoprostol for second trimester pregnancy termination among previous caesarian scar on uterus observed in his review of misoprostol induced abortions found that incidence of uterine Rupture was 0.4% and transfusion of blood was 0.2%, had success rate of 90.3%. In present study 2.5% had scar dehiscence and underwent Hysterotomy and 4% needed blood transfusion. Bhattacharyajee [11] quoted that medical abortion is not contraindicated in scarred uterus and results are comparable as in non-scarred uterus.

Chafika Mazouni, Magali provensal *et al.* [21], in the study with different dosage of misoprostol observed in second trimester termination of pregnancy among previous caesarian scar, the medical abortion failure rate of 0.5- 2% in Mifepristone and misoprostol groups of differing dosages, median induction Abortion interval (M I A I) was 8.5 hrs and 9.0 hrs respectively, no difference in amount of blood loss, retained placenta was higher with lower dose of misoprostol, 2 cases of scar dehiscence and scar rupture in lower dose of misoprostol, and no significant difference in incidence of excess haemorrhage in both groups [20]. incidence of retained placenta was higher with lower dose of misoprostol group-70% vs 52.5%, $p=0.25$). our experience was comparable to this study. Jan Elizabeth Dickinson [3] reported 3 cases of uterine rupture and placental retention 25% with Mifepristone and misoprostol regimen with mean IAI 9hrs, that is similar as in present study.

Shanthi shivkumar [22] *et al.* in their RCT with Mifepristone priming regimen followed by fourth hourly vaginal misoprostol with isosorbide nitrate Vs 4th hourly misoprostol -study observed that mean induction abortion Interval was 7 hrs in Misoprostol and isosorbide nitrate compared to 9hrs55min misoprostol group and no statistical difference in mean dosages administered. complete abortion rate was 94% vs 80%, side effects were less in isosorbide and misoprostol group 38% Vs misoprostol group 78%. In present study isosorbide and misoprostol had lesser complete abortion rate compared to control, as there was no prior dose of mifepristone given prior to second dose. Side effects were similar in present study and above study. Headche was more in isosorbide group. No other studies have been reported with single dose of isosorbide nitrate Vs prostaglandins regimen and prior studies had used various dosages and routes of prostaglandins and additional oxytocin along with misoprostol.

Mifepristone increased sensitivity of uterus to prostaglandins and caused more pain compared to lesser pain with isosorbide mono nitrate that causes cervical dilatation and softening without inducing uterine contractions. Hence isosorbide nitrate may be preferred in pregnancy termination on a scarred uterus. In conclusion, Mifepristone and misoprostol regimen is a safe, efficient with shorter duration in inducing second trimester Abortions but need to be used with caution in scarred uterus. Isosorbide mononitrate and misoprostol regimen is comparable in safety, efficacy, and has lesser pain and may be preferred in resistant cervix and as adjuvant for cervical preparation in previous Caesarian scar pregnancy.

5. Acknowledgements

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6. Conflict of interest

The authors have no conflicts of interest.

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