EVALUATION OF THE EFFICACY OF THE THREE REGIMENS OF VAGINAL MISOPROSTOL IN THE TERMINATION OF FIRST TRIMESTER PREGNANCY- A RANDOMISED CONTROLLED STUDY

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ABSTRACT

BACKGROUND

An abortion is the removal or expulsion of an embryo or foetus from the uterus, resulting in or caused by its death. Abortion in the first trimester is safe compared to the second trimester and medical methods are still safer than surgical techniques. Medical methods are safe, efficient and simple and result usually in complete abortion. Both Misoprostol and Mifepristone have been used singly in various doses and also in combination dosage schedule. There are many studies for both and each study claims its schedule to be superior and safer than others.

Aim: This study is done to compare the efficacy, complications and complete abortion rate of three different doses of vaginal misoprostol alone in first trimester MTP.

MATERIALS AND METHODS

This is a randomised controlled study. During the period 2004 - 2006, three hundred patients who attended the family planning clinic requesting for first trimester termination of pregnancy were selected at random based on the inclusion and exclusion criteria. Out of the three hundred patients, hundred each were assigned randomly to 200 micrograms, 400 micrograms and 600 micrograms group respectively. Patient was asked to empty the bladder and asked to lie down in the dorsal position with hips abducted and knees semiflexed. After cleaning and draping, a Sim's speculum was introduced into the vagina and posterior lip of cervix was caught with vulsellum.

- 200 micrograms of misoprostol were kept in the posterior fornix every 6 hourly for a maximum of four doses.
- 400 micrograms of misoprostol were kept every 8 hourly for a maximum of three doses.
- 600 micrograms were kept every 12 hourly for a maximum of two doses.

Three drops of distilled water were added to the tablet before keeping in the posterior fornix of vagina to facilitate the mucosal abortion. Patient was kept in the ward till the expulsion was complete- whenever necessary, check curettage was done. Complete abortion was confirmed with ultrasound. If no expulsion occurred after 24 hours, it was considered as a failure and other interventions were offered.

RESULTS

This study conducted at Government Kasturba Gandhi Hospital for Women and Children during the period 2004 – 2006, compares the efficacy of three different regimens of vaginal misoprostol in the first trimester termination of pregnancy. The results were subjected to statistical analysis using ANOVA with post-hoc test. 78% of the patients were in the age group of 21 - 30 years. 82% of cases were parous women, whereas only 18% of cases were nulliparous. Above 85% of the women in this study belonged to class IV/V socio-economic status. Though patients were selected at random, 73% of patients were 10 - 12 weeks pregnant. In this study induction, abortion interval was less with 600 micrograms of misoprostol. The I-A interval was least when the GA was 10 - 12 weeks. In this study complete abortion occurred in 41%, 52% and 74% of cases in 200 micrograms, 400 micrograms and 600 micrograms groups respectively. There is no significant difference in I-A interval between and within the parity by statistical analysis. There is statistically significant difference in complete and incomplete abortion between the three regimens, (p= 0.01 and 0.05). Statistically, there is significant difference in the incidence of side effects with the three regimens.

CONCLUSION

In this study, Induction-Abortion interval is less with 600 ug when compared to 400 ug and 200 ug. Induction-Abortion interval in 10 to 12 weeks of gestation observed in this is less. Complete abortion rate was more with 600 μg regimen when compared to other two regimens. Incidence of side effects was less with 200 ug. There was almost similar incidence of abdominal/ uterine cramps and excessive bleeding. Medical management of MTP is a boon to low resource countries like India where infrastructural facilities and trained personnel are at a premium. However, there is scope for misuse of this drug which needs to be curtailed and watched. This is a comparatively inexpensive, easy to administer technique which when used by properly trained persons in a setup with facilities for further management as and when required will go a long way in reducing the unwanted interferences by unscrupulous persons.

KEY WORDS

Abortion, Misoprostol, Pregnancy.

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BACKGROUND

An abortion is the removal or expulsion of an embryo or foetus from the uterus, resulting in or caused by its death. From historical times, termination of pregnancy was practiced with or without legal and social sanctions. The practice of induced abortion according to some anthropologists can be traced to ancient times.

Historically, pregnancies were terminated through a number of methods including the administration of abortifacient herbs, the use of sharpened instruments, camel dung, the application of abdominal pressure and other techniques.

Soranus, a second century Greek physician, suggested in his work of Gynaecology that women wishing to abort their pregnancies should engage in violent exercise, energetic jumping, carrying heavy objects and riding animals.

He also prescribed a number of recipes for herbal baths, pessaries and bloodletting, but advised against the use of sharp instruments to induce miscarriage due to the risk of organ perforation.

The ancient Greeks relied upon the herb Silphium, both as a contraceptive and an abortifacient. Such folk remedies, however varied in effectiveness and were not without risks. Tansy and Pennyroyal are two poisonous herbs with serious side effects that have at times been used to terminate pregnancies.

Because of its greater safety nowadays and great impact on population control, abortion has gained tremendous popularity in the last few decades to get rid of undesired pregnancy.

In fact, it is difficult for any country to reduce its population growth without recourse to pregnancy termination. That is why more and more countries are liberalising their abortion laws. 3.1 lakh legal abortions are being performed every year with an abortion rate of 2.3/1000 women. 4.46 million illegal abortions are being performed every year with an abortion rate of 130 to 200/1000 women. In India, the mortality due to criminal abortion is 500/100000.

Unsafe abortions account for 9 percent of maternal deaths in India. Safe abortion services as provided by law should be easily available-

- By well-trained health care providers.
- Regulation of health system.
- Infrastructure including equipment and supplies.

Abortion in the first trimester is safe compared to the second trimester and medical methods are still safer than surgical techniques. Medical methods are safe, efficient and simple and results usually in complete abortion.

Both Misoprostol and Mifepristone have been used singly in various doses and also in combination dosage schedule.[1,2,3]

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There are many studies for both and each study claims its schedule to be superior and safer than others.

This study is done to compare the efficacy, complications and complete abortion rate of three different doses of vaginal misoprostol alone in first trimester MTP.

In this randomised controlled study, three different dose schedules of misoprostol through the same route of application are analysed as to its efficacy in successfully affecting termination in the lowest possible time with no mortality and no or minimal morbidity.

This study conducted at Government Kasturba Gandhi Hospital for Women and Children, Triplicane, Chennai during the period 2004 - 2006 compares the efficacy of three different regimens of vaginal misoprostol 200, 400 and 600 micrograms in first trimester termination of pregnancy.

MATERIALS AND METHODS

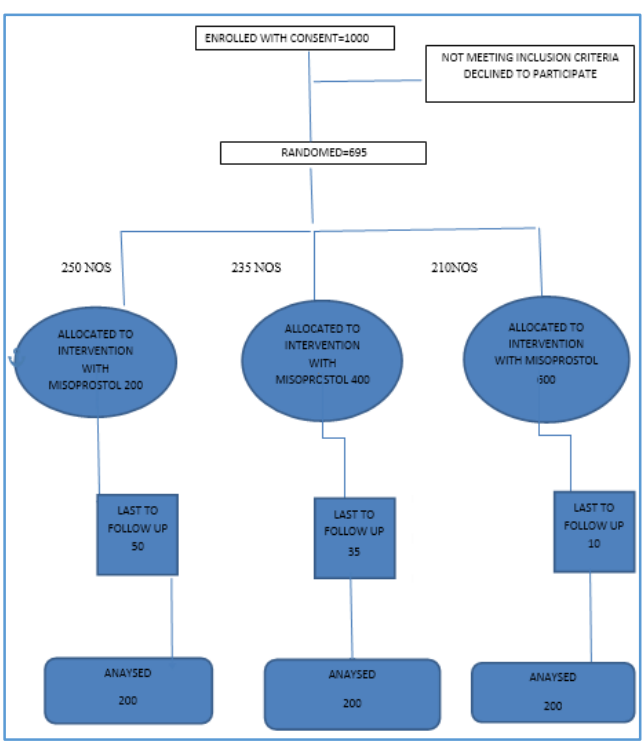
This is a randomised controlled study done during the period of 2004 - 2006.

Study Setting

This study was conducted at Government Kasturba Gandhi Hospital for Women and Children, Triplicane, Chennai.

Three hundred patients who attended the family planning clinic at Govt. Kasturba Gandhi Hospital, Triplicane requesting for first trimester termination of pregnancy were selected based on the inclusion and exclusion criteria. Sample size was taken as per our convenience. Patients were randomised using computerised randomisation table and were allocated into three groups.

Out of the three hundred patients, hundred each were assigned randomly by lots to 200 micrograms, 400 micrograms and 600 micrograms group respectively according to the Flow Chart.



Patient Selection

Inclusion Criteria

- Confirmed pregnancy up to 12 weeks.
- Single live intrauterine gestation.
- No previous surgery in the uterus.
- Contraceptive failure.
- No other medical or surgical contraindications for the procedure.
- Medical termination of pregnancy for social and eugenic causes.

Exclusion Criteria

- Women aged more than 35 years.
- Parity more than G3.
- Heavy smokers (smoking more than 10 cigarettes per day).
- Suspected or proven ectopic pregnancy.
- Inevitable incomplete/ Missed abortion.
- Allergy or intolerance to misoprostol.
- Previous history of medical disorders like cardiac disease/ diabetes/ asthma/ epilepsy/ psychiatric disorder.
- Any previous attempts at terminating the present pregnancy.
- Uncontrolled hypertension.
- Severe liver disease/ chronic adrenal failure.
- Anaemia, Hb < 8 g%.

Methods

All these women were thoroughly investigated before performing medical termination of pregnancy. The workup included-

- Details of the patient (Name, Age, Address, Height, Weight).
- Menstrual/ Marital/ Obstetric history.
- Medical/ Surgical history.
- Investigations.
- General examination.
- Examination of vital signs.
- Abdominal and pelvic examination.
- Ultrasound only on indication.
- Counselling.

Such patients who were willing to adhere to the protocol were included for the study. Each group has hundred patients.

All these women were informed about the procedure. An informed consent was obtained from these selected women.

Procedure

Patient was asked to empty the bladder and asked to lie down in the dorsal position with hips abducted and knees semiflexed.

After cleaning and draping, a Sim's speculum was introduced into the vagina and posterior lip of cervix was caught with vulsellum.

Dosage Schedule

- 200 micrograms of misoprostol were kept in the posterior fornix every 6 hourly for a maximum of four doses.
- 400 micrograms of misoprostol were kept every 8 hourly, for a maximum of three doses.
- 600 micrograms were kept every 12 hourly for a maximum of two doses.

Three drops of distilled water was added to the tablet before keeping in the posterior fornix of vagina to facilitate the mucosal absorption. Patient was kept in the ward till the expulsion was complete- whenever necessary, check curettage was done. Complete abortion was confirmed with ultrasound.

If no expulsion occurred after 24 hours, it was considered as a failure and other interventions offered. Patients were advised about the symptoms like-

- Nausea/ vomiting and diarrhoea.
- Headache.
- Excessive bleeding.
- Abdominal cramps.
- Dizziness.
- Data management.
- The variables: age, parity, socio-economic status and gestational age.
- Socio-economic status is calculated with the help of income, education and occupation.

Statistical Analysis

Data was analysed using SPSS 16.0. The qualitative data were expressed as numbers and percentages. The continual variables expressed as mean and standard deviation. Mean and Standard deviation were compared using one-way ANOVA with post hoc test. Chi-square test was used to find difference between the three different groups.

RESULTS

This study conducted at Government Kasturba Gandhi Hospital for Women and Children during the period 2004 - 2006 compares the efficacy of three different regimens of vaginal misoprostol in the first trimester termination of pregnancy. (The results were subjected to statistical analysis using ANOVA with post hoc test (Analysis of variance test), other variables were also compared statistically.)

Age Group	Misoprostol 200 µg		Misoprostol 400 µg		Misoprostol 600 µg		P value
	No. of Cases	%	No. of Cases	%	No. of Cases	%	
< 20	7	7	9	9	7	7	0.954
21-25	37	37	38	38	35	35	
26-30	40	40	42	42	43	43	
> 30	16	16	11	11	15	15	

Table I. Age Distribution

78% of the patients were in the age group of 21-30 years.

14% were in the age group 30 and above.

Only less than 10% of the patients were in the age group of 16-20 years.

Parity	Misoprostol 200 µg		Misoprostol 400 µg		Misoprostol 600 µg		P value
	No. of Cases	%	No. of Cases	%	No. of Cases	%	
UMP	2	2	1	1	2	2	0.985
G1	16	16	14	14	14	14	
G2	39	39	43	43	44	44	
G3	43	43	42	42	40	40	

Table II. Parity

- Unmarried pregnancies were only 2% in the three groups.
- Primigravida were about 15% in the three groups, whereas parous women were about 82%.
- Above 86% of the women belonged to socioeconomic status class IV/V.
- Only 3% of the women belonged to class I/II socio-economic status.
- In class III socio-economic status group, there were about 12% of women.
- 73% of the patients belonged to 10 - 12 weeks gestational age group.
- 19% of the patients were in the gestational age group of 7 - 9 weeks.
- Only 8% of the women belonged to less than 7 weeks gestational age group.

Characters		Misoprostol 200 µg	Misoprostol 400 µg	Misoprostol 600 µg
Parity	UMP	24.00	22.30	18.00
	G1	23.20	20.00	17.00
	G2	22.30	20.00	16.30
	G3	22.00	19.30	16.30
Gestational Age	< 7 weeks	24	22.30	21.30
	7 - 9 weeks	22.45	21.00	17.30
	10 - 12 weeks	22.00	19.30	16.00

Table III. Induction-Abortion Interval in Hours

UMP- Unmarried pregnancies

- The I-A interval was lowest if the GA was 10 - 12 weeks irrespective of the parity.

Misoprostol 200 µg				Misoprostol 400 µg				Misoprostol 600 µg			
Incomplete Abortion		Method Failure		Incomplete Abortion		Method Failure		Incomplete Abortion		Method Failure	
No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
10	10	3	3	9	9	2	2	4	4	2	2
38	38	8	8	31	31	6	6	15	15	5	5

Table IV. Complete Abortion

- Complete abortion occurred in 41% of cases in 200 micrograms group and in 52% of cases in 400 micrograms group.
- Complete abortion was higher in 600 micrograms group. It occurred in 74% of cases.

Side Effects	Misoprostol 200 µg		Misoprostol 400 µg		Misoprostol 600 µg	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
Symptom Free	28	28	19	19	10	10
Vomiting	27	27	35	35	41	41
Diarrhoea	1	1	2	2	5	5
Abdominal/ Uterine Cramps	18	18	18	18	16	16
Excessive Bleeding	26	26	25	25	26	26
Dizziness	0	0	1	1	2	2

Table V. Side Effects

- Symptoms were less with 200 micrograms group.
- Vomiting was higher in 600 micrograms group (41%), whereas it was noted only in 27% of cases in micrograms group.
- Only one case had diarrhoea in 200 micrograms group. 2% in 400 micrograms group and 5% in 600 micrograms group had diarrhoea.
- Onset of abdominal/ uterine cramps and excessive bleeding were almost similar in all three groups.
- None of them in 200 micrograms group had dizziness.
- Only 1% in 400 micrograms group and 2% in 600 micrograms group had dizziness.

Statistical Analysis of Results

Dose in Micrograms	N	Mean	Standard Deviation	P value
200	41	22.22	.613	< 0.0001
400	52	19.57	.936	
600	74	16.59	2.024	

Table VI. Analysis of Induction-Abortion Interval in Hours

N- No. of complete abortion

- The mean induction-abortion interval in 200 µg, 400 µg and 600 µg group is 22.22 hours, 19.57 hours and 16.59 hours respectively.
- By ANOVA with post hoc test (Analysis of Variance), there is a significant difference in induction/abortion interval between the three different groups and within the groups and p value is < 0.0001.

Gestational Age	Group 1	Group 2	Group 3	P value
	Mean ± S.D	Mean ±S.D	Mean ±S.D	
< 7 weeks	23.94 ± 1.19	23.66 ± 1.98	22.36 ± 2.05	0.157
7-9 weeks	23.59 ± 1.81	22.39 ± 1.89	18.50 ± 2.84	<0.0001
10-12 weeks	22.38 ± 1.01	19.79 ± 1.30	16.64 ± 2.63	<0.0001
P value	<0.0001	<0.0001	<0.0001	

Table VII. Analysis of Induction-Abortion Interval in Gestational Age

Gestational Age	Group 1	Group 2	Group 3	P value
	Mean ± S.D	Mean ± S.D	Mean ± S.D	
UMP	18.65 ± 1.90	14.00 ± 0	16.65 ± 1.90	0.332
G1	16.79 ± 3.15	21.24 ± 2.25	18.42 ± 4.25	0.003
G2	16.92 ± 3.21	20.40 ± 2.55	16.92 ± 3.21	<0.0001
G3	22.17 ± 0.99	20.10 ± 1.72	17.25 ± 2.88	<0.0001
P value	<0.0001	0.014	0.565	

Table VIII. Analysis of Induction-Abortion Interval in Parity

UMP- Unmarried pregnancies

	Complete Abortion	Incomplete Abortion	P value
Misoprostol 200 µg	41	48	<0.0001
Misoprostol 400 µg	52	40	
Misoprostol 600 µg	74	19	

Table IX. Analysis of Complete/Incomplete Abortion

Statistical analysis shows there is a significant difference in success rate of complete abortion between the three regimens of misoprostol and p-value is 0.01.

There is statistically significant difference in incomplete abortion between the three regimens with a p-value of 0.05.

Side Effects	Vomit-ing	Diar-rhoea	Abdominal/ Uterine Cramps	Excessive Bleeding	Dizziness
Misoprostol 200 µg	27	1	18	26	0
Misoprostol 400 µg	35	2	18	25	1
Misoprostol 600 µg	41	5	16	26	2
P value	0.112	0.188	<0.0001	0.342	<0.0001

Table X. Statistical Analysis of Side Effects

By statistical analysis (Correlation) of side effects of the drug revealed the following results- 16.8% symptom free, 41.9% vomiting, 19.2% abdominal/uterine cramps, 18.6% excessive bleeding, 2.4% diarrhoea and 1.2% dizziness.

Among the three dosage groups there is statistically significant difference in the incidence of side effects, vomiting [6%, 15.6%, 20.4%], diarrhoea [0.0%, 0.6%, 1.8%], abdominal/uterine cramps (7.8%, 6.0%, 5.4%), excessive bleeding (3.0%, 4.2%, 11.4%), dizziness (0.0%, 0.6%, 0.6%) between 200, 400 and 600 µg respectively.

DISCUSSION

This study comparing the efficacy of three different regimens of vaginal misoprostol in the termination of first trimester of pregnancy was undertaken in 300 patients.

The Results of this study were discussed as follows-

Table I: 78% of the patients were in the age group of 21-30 years.

Table II: 82% of cases were parous women, whereas only 18% of cases were nullipara.

Table III: Above 85% of the women in this study belonged to class IV/ V socioeconomic status.

Table IV: Though patients were selected at random, 73% of patients were 10 - 12 weeks pregnant.

Table V: In this study induction-abortion interval was less with 600 micrograms of misoprostol. The I-A interval was least when the GA was 10 – 12 weeks.

Table VI: In this study complete abortion occurred in 41%, 52% and 74% of cases in 200 micrograms, 400 micrograms and 600 micrograms groups respectively. The success rates were different in different studies using different route of administration and doses. A study by Koopersmith and Mishell 1996 showed the success rate of 50% when 200 micrograms was used and 60% when the dose was 400 micrograms.[4,5,6,7] Success rate of 81% of complete abortion with 800 ug [Esteve JL et al 1998] at 24 hours interval.[8,9,10,11] Success rate is 97% complete abortion using 800 micrograms at 24 hours interval (Jain, Mekstrath, Lacarrt 1998). 84% of complete abortion occurred when 800 micrograms were used at 24 hours interval by Carbonell et al 2001.[12,13,14,15] Ngai et al showed success rate of 85% complete abortion using 800 micrograms of misoprostol at 48 hours interval.

Table VII: In this study, 27% of women in the 200 micrograms group had vomiting. Other side effects reported were uterine/abdominal cramps (18%), excessive bleeding (26%) and diarrhoea (1%). Study by Bugalho et al reported nausea (19%), vomiting (6%), diarrhoea (7%), fatigue (12%) and lower abdominal pain (71%).[16,17,18] In this study 400 micrograms group women experienced the following side effects, viz. vomiting (35%), excessive bleeding (25%), abdominal cramps (18%), diarrhoea (2%) and dizziness (1%). When compared to other two groups 41% of women in 600 micrograms group experienced vomiting, 16% uterine cramps, 5% diarrhoea and 2% dizziness. Various studies conducted by Carbonell et al [1999 - 2000] using different doses at different intervals showed varying side effects.[19,20,21]

Nausea (22%), vomiting (17%), diarrhoea (54%), dizziness (25%), headache (19%), fever (26%), pelvic pain (99%) experienced by women using 800 micrograms misoprostol (Carbonell, Fernandez C, et al 1998).[22,23,24,25]

Table VIII: Mean induction-abortion interval in 200 ug, 400 ug and 600 ug is 22.22, 19.57 and 16.59 respectively. Maximum interval is 24, 22 and 21 respectively. Bebbington, Michael W et al AJOG reported that induction-abortion interval with the vaginal route was less (24 hours)[26,27,28] when compared with oral route with a statistically significant difference of 0.01. Study by F Dong et al (BJOG) using 800 µg of vaginal misoprostol reported that the mean interval between first dose of misoprostol and the onset of expulsion of products of conception (SD) as 8.1 hours.[29,30,31]

Table IX: There is a statistically significant difference in I-A Interval between the three dosage groups and p value of 0.000.

Table X: Difference in I-A interval between the three gestational age groups is statistically significant and p-value is 0.027. Surg. Capt. Sushil Kumar et al reported success rate of 67% using 800 µg vaginal misoprostol at < 8 weeks and 83% at 8 - 12 weeks.[32,33]

Table XI: There is no statistically significant difference in I-A interval in parity and p-value of 0.233.

Table XII: There is statistically significant difference in success rate of complete and incomplete abortions with a p-value of 0.01 and 0.05. A WHO multicentric trial (1998 - 2000) using three misoprostol regimens after pre-treatment with mifepristone showed success rate of 96 - 98% in all the groups.

Table XIII: Statistically significant difference is observed in incidence of side effects in the three dosage groups. Hamoda, Ashok et al, AJOG reported nausea p= .008), diarrhoea (p=0.01) and unpleasant mouth taste (p= 0.0001) in sublingual group compared with women in the vaginal route.[34,35] In a study by Mittal, Kumar et al more women experienced vaginal bleeding, abdominal pain and shivering in the 400µg misoprostol group compared with the 200 ug

misoprostol group with a statistically significant difference ($p<0.05$).

Summary

This present randomised controlled study conducted at Government Kasturba Gandhi Hospital for Women and Children, Chennai during the period 2004 - 2006 evaluated the efficacy of the three regimens of vaginal misoprostol in the termination of first trimester of pregnancy.

A total of 300 women who attended the family planning clinic requesting for first trimester termination of pregnancy were included in the study.

The efficacy of three regimens of vaginal misoprostol was compared in terms of Induction-Abortion interval, complete abortion, incomplete abortion and incidence of side effects and the results were statistically analysed. Observations in this study include-

- Most of the patients were in the age group of 21 - 30 years (78%).
- 82% of the women were parous, only 18% were nullipara.
- Most of the women belonged to class IV/V socioeconomic status (85%).
- 73% of the patients belonged to 10 - 12 weeks of gestation, though they were selected at random basis.
- In the study, I-A interval was less (16.30 hours) with 600 micrograms.
- Complete abortion varied in the three groups and was highest in 600 micrograms group (74%).
- Side effects were less in women who received 200 ug. None of the women in this group had dizziness and only one patient had diarrhoea. Incidence of bleeding was similar in all the three groups.
- Mean I-A interval using 200 micrograms was 22.22 hours with 400 micrograms it was 19.57 hours and with 600 micrograms 16.59 hours.
- Statistically, there is a significant difference in I-A interval between and within the three dosage groups ($p= 0.000$).
- There is also a statistically significant difference in I-A interval between and within the gestational age groups ($p= 0.027$).
- There is no significant difference in I-A interval between and within the parity by statistical analysis.
- Statistically significant difference is there in complete and incomplete abortion between the three regimens. ($p= 0.01$ and 0.05).
- Statistically, there is significant difference in the incidence of side effects with the three regimens.

CONCLUSION

- Induction-Abortion interval is less with 600μg when compared to 400μg and 200μg.
- Induction-Abortion interval in 10 - 12 weeks of gestation observed in this is less.
- Complete abortion rate was more with 600μg regimen when compared to other two regimens.
- Incidence of side effects was less with 200μg.
- There was almost similar incidence of abdominal/ uterine cramps and excessive bleeding.

Medical management of MTP is a boon to low resource countries like India, where infrastructural facilities and trained personnel are at a premium. However, there is scope for misuse of this drug, which needs to be curtailed and watched. This is a comparatively inexpensive, easy to administer technique, which when used by properly trained persons, in a setup with facilities for further management as and when required, will go a long way in reducing the unwanted interferences by unscrupulous persons.

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