THE TAMIL NADU Dr. MGR MEDICAL UNIVERSITY

CHENNAI –TAMIL NADU

DISSERTATION

"A COMPARITIVE STUDY OF EFFICACY OF THREE DIFFERENT REGIMENS OF VAGINAL MISOPROSTOL IN FIRST TRIMESTER TERMINATION OF PREGNANCY"

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CERTIFICATE

This is to certify that this Dissertation entitled,

"A COMPARITIVE STUDY OF EFFICACY OF THREE DIFFERENT REGIMENS OF VAGINAL MISOPROSTOL IN FIRST TRIMESTER TERMINATION OF PREGNANCY" is the bonafide record work done by **Dr. R. SUCHINDRA**, submitted as partial fulfillment for the requirements of M.D.(Obstetrics and Gynecology) Degree Examinations Branch II, March, 2007.

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GLOSSARY

MTP	**-**	**Medical Termination of Pregnancy**
UMP	**-**	**Unmarried Pregnanacy**
GA	**-**	**Gestational Age**
I-A	**-**	**Induction – Abortion Interval**
μg	**-**	**Microgram**

INTRODUCTION

DEFINITION:

An Abortion is the removal or expulsion of an embryo or fetus 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.

HISTORY OF ABORTION

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 Gynecology 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 blood letting, 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.

Infact it is difficult for any country to reduce its population growth without recourse to pregnancy termination. That is why more and more countries are liberalizing their abortion laws.

GLOBAL ABORTION SCENARIO

An estimated 46 million pregnancies end in induced abortions each year (World Health Organization).

Nearly 20 million of these are estimated to be unsafe, 95 percentage of these occur in developing countries (World Health Organization 1998). About 13% of pregnancy related deaths have been attributed to complications of unsafe abortion (World Health Organization 1998).

When applied to the most recent estimate of maternal death this percentage corresponds to 67,000 deaths annually (World Health Organization 2001).

Globally there is a ratio of one unsafe abortion for every seven live births (World Health Organization 1998).

The risk of death from legal abortion is about 0.4/100000 induced abortions, whereas the maternal mortality is approximately 7 to 8/ 100000 live births.

INDIAN ABORTION SCENARIO

3.1 lakh legal abortions are being performed every year with an abortion rate of 2.3/ 1000 women. 4.6 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. (9)

Safe abortion services as provided by law should be

* Easily available
* By well trained health care providers
* Regulation of health system
* Infrastructure including equipments and supplies.

METHODS AVAILABLE FOR FIRST AND SECOND TRIMESTER MTP

FIRST TRIMESTER:

1. Menstrual regulation
2. Manual/ electrical vacuum aspiration
3. Dilatation and curettage
4. Laminaria tent and prostaglandins for cervical dilatation.
5. Medical methods.

SECOND TRIMESTER :

1. Extra amniotic instillation of ethacridine lactate 1% or 2%.
2. Intra amniotic instillation of various agents.
3. Prostaglandins.
4. Mechanical devices like laminaria tents, catheters
5. Aspirotomy
6. Hysterotomy.

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. (27)(28)(29).

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

REVIEW OF LITERATURE

Termination of pregnancy is now permitted on broadly interpreted medical, psychological and social grounds. In India, the Medical termination of pregnancy (MTP) act was passed by the parliament in 1971 and came to force on 1st April 1972.

To reduce high maternal mortality associated with abortion, government of India setup

- Shanthilal Shah committee in 1964, which recommended liberalization of abortion law to decrease maternal mortality rate.
- Bill presented in Rajya Sabha and Lok Sabha in 1969

- Act passed by parliament in August 1971, implemented in April 1972 all over India.
- The act was amended in December 2002 and rules in June 2003.

Medical termination of pregnancy in India is permitted under the law up to 20 weeks of gestation but not beyond.

INDICATIONS ON WHICH PREGNANCY MAY BE TERMINATED:

1.Medical Grounds:

When continuation of pregnancy is likely to endanger the life of the pregnant women.

Cause grievous injury to her physical and medical health as in case of severe hypertension, severe cardiac diseases, diabetes, psychiatric illness, and genital or breast cancer.

2. Eugenic Grounds:

Substantial risk of the child being born with serious physical or mental abnormalities.

3. Humanitarian Grounds:

Pregnancy is caused by rape or incest.

4. Social Grounds:

Risk of injury to mental health of pregnant women. Pregnancy resulting from failure of contraceptive device or method.

Persons who can perform MTP:

Registered medical practitioner having postgraduate training or qualification in obstetrics and gynecology.

Registered medical practitioner having been trained for six months at a specialized and recognized training center for MTP.

***Upto 12 weeks*:**

Practitioner who has assisted registered medical practitioner in the performance of 25 cases of MTP, of which at least five has been performed independently in a hospital established or maintained by the government.

***Upto 20 weeks*:**

A practitioner should hold a Post-graduate degree/Diploma in Obstetrics and gynecology.

A practitioner who has completed six months of internship in Obstetrics and gynecology or at least one year of experience in obstetrics and gynecology.

PLACE FOR PERFORMING MTP:

1. All hospitals established and maintained by the government
2. At places recognized and approved by the government under the MTP act.

These rules in existence since 1972 were amended in 2002 and 2003 to incorporate some newer requirements to MTP and also to plug the lacunae and loopholes in the existing act.

HIGHLIGHTS OF NEW RULES ARE

i. Composition and tenure of district level committee.

ii. One member of district level committee shall be gynecologist / surgeon/ anesthetist

iii. Other members from the local medical profession, non-governmental organization and panchayat institution.

iv. At least one member of the committee should be a woman.

The tenure of the committee would be for two calendar years and the tenure of the NGO member shall not be for more than two terms.

IMPLICATIONS OF THE MTP ACT:

In countries with liberal abortion laws maternal morbidity and mortality have declined and women have been motivated to accept birth control measures (World Health Organization).

Repeated abortions are not conducive to a woman's health, hence MTP should not be considered as a birth control measure and should not replace the prevailing methods of contraception.

Even the best of circumstances there is a small inherent risk in the procedure of MTP. The woman undergoing MTP should be educated to accept contraception.

Thus MTP can indirectly promote family planning and population control.

UNSAFE ABORTION:

An unsafe abortion is a procedure for terminating an unwanted pregnancy either by persons lacking the necessary skills or in an environment lacking the minimal medical standards or both (World Health Organization, 1992).

Safe abortion save women's lives and avoids the often-substantial costs of treating preventable complications of unsafe abortion (Fortney 1981, Tshibangu et al 1984, Figa Talamanca et al 1986, Mpangile et al 1999).

MEDICAL METHODS OF FIRST TRIMESTER ABORTION:

- Prostaglandins [Misoprostol, Gemeprost]
- Mifepristone [RU 486]
- Methotrexate
- Mifepristone with prostaglandin analogues.

Medical methods of aborion have been proved to be safe and effective [Winikoff et al 1997, Ashok et al 1998a, Peyron et al 1993] (15) (28)

MISOPROSTOL

Misoprostol is a synthetic prostaglandin E1 analogue. It is a 17 methyl-[3 hydroxy-2(4 hydroxyl-4methyl-oct-1enyl)-5oxo-cyclopentylheptanoate]

CHEMICAL FORMULA: $C_{22}H_{38}O_5$

It is available as tablets containing 200 or 100 microgram of the drug

Each tablet has

- Hydrogenated castor oil
- Hydroxypropyl methyl cellulose
- Microcrystalline cellulose
- Sodium starch glycolate

ROUTES OF ADMINISTRATION:

Oral, vaginal, sublingual, rectal and buccal.

ADVANTAGES:

- It is inexpensive
- It is easily stored (shelf life 7 years)
- In comparison with other prostaglandins, minimal effects on cardiovascular and bronchial tree smooth muscle.
- Is not affected by ambient temperature
- Needs no refrigeration for its storage and administration.

Uses of Misoprostol:

- For prevention and treatment of peptic ulcer.
- For first and second trimester termination of pregnancy
- Induction of labor (not yet approved)
- Prevention and management of post partum hemorrhage (14)
- Erectile dysfunction. (35)

MECHANISM OF ACTION OF MISOPROSTOL:

Misoprostol inhibits gastric acid secretion, promotes bicarbonate secretion and increases mucosal blood flow. It is mucoprotective and hence it is used in drug induced peptic ulcer.

Prostaglandins are naturally occurring fatty acids produced by many tissues in the body. Prostaglandin E_1 causes myometrial contractility by interacting with specific receptors on myometrial cells.

This interaction results in a cascade of events including a change in calcium concentration thereby initiating muscle contraction.

Misoprostol, analogue of PGE_1 by interacting with prostaglandin receptors causes the cervix to soften and the uterus to contract resulting in the expulsion of the uterine contents.

Misoprostol is metabolically resistant and thus has prolonged action For induction of abortion, misoprostol is as effective as gemeprost and is a better alternative than mifepristone

PHARMACOKINETICS:

Misoprostol is rapidly absorbed after oral, vaginal and rectal administration. It is metabolized by de-esterification to misoprostol acid, then to prostaglandin F analogues.

With oral administration the half life is less than 30 minutes, and peak level is at 15 minutes. After vaginal administration, there is a gradual rise to a maximum level at 60-120 minutes, but at 240 minutes the level is still at 60% of peak level.

Excretion: Renal- 80%,

Fecal- 15%

Vaginal application is better than oral route for MTP.

Drug Interactions:

Antacids

Cyclosporine

These drugs result in reduced bio-availability of misoprostol. Vaginal administration of citric acid may prove beneficial for misoprostol absorption.

SIDE EFFECTS: [*Faunders,1996, Haberal,1996 Ayres-de-Campos,2000] (1) (12) (13))*

Nausea,

Vomiting,

Diarrhea

Headache

Hypotension

Excessive bleeding

Uterine cramps

Failure to cause abortion and subsequently delivered babies showed increased incidence of congenital defects like talipes equinovarus, cranial nerve defects, arthrogryposis (*Claudetta et al1998*), mobius syndrome (*Pastuszak et al 1998*)(11).

CONTRAINDICATIONS:

1. Cardiovascular diseases- Angina, valvular heart disease.
2. Sickle cell anemia
3. Coagulopathies
4. History or evidence of thromboembolism
5. Liver disease
6. Severe renal disease
7. Ectopic pregnancy
8. Presence of IUCD in-utero
9. Uncontrolled seizure disorder
10. Heavy smoker
11. Allergy to Misoprostol
12. Uncontrolled hypertension
13. Adrenal failure.
14. Undiagnosed adnexal diseases.

Blanchard K et al, 1999 states that a vaginal misoprostol regimen as opposed to an oral regimen improves access to safe medical abortion services in developing countries.

(*Blanchard K et al, 1999) (16)*

Study by *Bugalho et al* comparing 200 microgram with 400 microgram of vaginal misoprostol for a total of four doses every 12 hours shows success rate of 46% for 5-7 week group and 45% for 8-11 week group receiving 200 microgram and 55% for 5-7 week group and 67% for 8-11 week group receiving 400 microgram.

(*Bugalho et al, 1996)* (17)

Crenin(18) and Vittinghoff tried 800 microgram of misoprostol up to maximum total dose of 1600 microgram vaginally 24 hours apart with pregnancies less than or equal to 56 days gestation and showed success rate of 47%.

Koopersmith and Mishell 1996 (20) conducted study on 4 different misoprostol only regimens vaginally, using 200 microgram every 8 hours with a success rate of 50% with another regimen using 400 microgram initially followed

by 200 microgram every 8 hours upto a total maximum dose of 1400 microgram showing a success rate of 100%.

Another regimen using an initial dose of 400 microgram followed by 200 microgram every 4 hours up to a total maximum dose of 1200 microgram showed success rate of 60%.

Yet another regimen using an initial oral dose of 400 microgram plus 400 microgram vaginally every 8 hours up to a total maximum dose of 1600 microgram with a success rate of 60%.

Jain J K et al 1998 (19), studied two doses of 800 microgram misoprostol vaginally 24 hours apart in women with gestational age of less than or equal to 56 days with a success rate of 97%.

Carbonell et al conducted various studies using different doses of vaginal misoprostol that include

1. *carbonell et al 1997a* (3) using 800 microgram of vaginal misoprostol every 48 hours along with additional doses of misoprostol depending upon the amount of remains present in the uterus as determined by ultrasound and showed a success rate of 94%.

2. *Carbonell JLL et al 1997b(4)* studied 800 microgram of vaginal misoprostol administered every 48 – 96 hours upto a total maximum doses of 2400 microgram plus additional dose of 600 microgram for remains in the uterus and showed a success rate of 94%.

3. *Carbonell Esteve JL, Varela L et al 1998(6)* tried three doses of 800 microgram of misoprostol vaginally 24 hours apart (plus additional dose of 600 microgram for the amount of remains in the uterus) in women with pregnancies of 64-84 days gestation with a success rate of 87% complete abortion.

4. *Carbonell, Varela L, Velazco A et al, 1999* (7) studied 800 microgram of misoprostol administered 12- 24 hours apart showed a success rate of 85% complete or partial and at intervals of 48 – 96 hours apart showed a success rate of 89% complete abortion.

5. *Carbonell et al, 2000 (8)* studied 600 microgram of vaginal misoprostol upto a maximum of 3 doses every 24 hours with a success rate of 64%.

Studies by *Ngai SW et al* 2000 (21) using 800 microgram of

misoprostol administered 24 – 48 hours apart shows success rate of 85%.

Tang and Ho et al (23) tried 600 microgram of misoprostol upto maximum of 5 doses sublingually with a success rate of 100%.

Study by *Kuldipsingh et al* BJOG (37) with an initial dose of 800 microgram of vaginal misoprostol and a further dose of 400 microgram repeated every three hours for a maximum of three doses showed success rates between 84.7% and 96%.

Study by *Zieman, Benowitz et al* shows that the bio-availability of vaginal misoprostol is three times higher than orally administered misoprostol and suggests that vaginal administration could be dosed at longer intervals.

Ekerhovd E, et al 2003 (26) conducted a study comparing the efficacy of 400 microgram of misoprotol with that of 1mg of Gemeprost for cervical priming three to four hours before surgical termination of first trimester pregnancies concluded that vaginal misoprostol was as effective as gemeprost.

Norman et al 1991,(22) conducted a study using single dose of 400 microgram of misoprostol with a success rate of only 5%.

Study by zikopoulos KA, Papanikolaou EG et al using 800 microgram of vaginal misoprostol, repeated every 24 hours for a maximum of three doses showed a success rate between 86.3% to 96.3%.

Study by Ozeren M.Bilekli et al using misoprostol and methotrexate alone or in combination for early abortion in the dosage of 50 mg/sq.m. of methotrexate followed by varying doses of misoprostol (400 μg to 800 μg) showed success rate between 69% to 86%.

METHOTREXATE:

Methotrexate (both oral and intramuscular combined with misoprostol have been under investigation since 1993 with complete abortion rates similar to mifepristone regimen for pregnancies upto 49 days gestation. (Crenin MD et al 2000).

50mg /m2 body surface area of methotrexate followed by 800µg of misoprosol from day 3 to day 7 have shown to results in complete abortions in 83 to 96% of cases. (crenin MD et al and other studies)

In 20 to 30% of women, abortion using methotrexate and misoprostol takes longer and may take upto 5 weeks.

Use of methotrexate for first trimester abortion is only of academic interest since WHO toxicity panel recommended against methotrexate use due to its teratagenicity.

MIFEPRISTONE :

It is an anti-progestin, acts by binding with progesterone receptor and inhibits the action of progestin, hence interfere with continuation of pregnancy.

After confirming the eligibility to undergo medical abortion 600 mg of mifepristone is administered orally on day 1.

On day 3, the patient is assessed for the possibility of pregnancy expulsion which occurs only in 2-5% of patients with mifepristone alone.

MIFEPRISTONE WITH PROSTAGLANDIN ANALOGUES

600 mg of mifepristone orally on day 1 followed by prostaglandin analogues on day 3 has been associated with a success rate of 95%.

(Trusell Elterson 1989)

In order to reduce the cost of 600 mg of mifepristone lower dose was tried. Later it was thought that 200 mg of mifepristone is as efficacious as 600 mg of mifepristone (Mc Kinley et al 1993)

Mifepristone in the doses of 200 mg, 400 mg and 600 mg were tried followed by a vaginal gemeprost 48 hours later. The success rate of the above dosage regimens was found to be 93.8%, 94.1% and 94.3% respectively.

The overall continuation of pregnancy rate was 0.4% in all the regimens (WHO task force on post ovulatory method of fertility, BMJ, 1993).

SURGICAL METHODS:

Two types of surgical procedures are performed

1. Vacuum aspiration
2. Dilatation and evacuation (also called Dilatation and curettage)

COMPLICATIONS OF SURGICAL METHODS:

- Uterine hemorrhage
- Pelvic infection
- Cervical injury
- Uterine perforation
- Retained products (incomplete abortion)
- Continuation of pregnancy
- Anesthetic complications.

Subsequent hemolytic disease of the newborn can be prevented by administration of 50 microgram of Rh immunoglobulin to all Rh negative women undergoing abortion in the first trimester.

AIM OF THE STUDY

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

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 given below.

Out of the three hundred patients, hundred each were assigned randomly to 200 microgram, 400 microgram and 600 microgram group respectively.

PATIENTS SELECTION

INCLUSION CRITERIA:

- Confirmed pregnancy upto 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:

- Gestational age more than 12 weeks
- 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.
- History or evidence of thromboembolism

- Any previous attempts at terminating the present pregnancy
- Coagulation disorders
- Uncontrolled hypertension
- Severe liver disease / chronic adrenal failure
- Anemia, Hb < 8 g%.

METHODS

All these women were thoroughly investigated before performing medical termination of pregnancy. The work up 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
- ❖ Counseling

Such of those patients who were willing to adhere to the protocol were included for the study, provided they fulfilled the inclusion criteria.

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 drapping, a Sim`s speculum was introduced into the vagina and posterior lip of cervix was caught with volsellum.

Dosage schedule:

- 200 microgram of misoprostol was kept in the posterior fornix every 6^{th} hourly for a maximum of four doses.
- 400 microgram of misoprostol was kept every 8^{th} hourly, for a maximum of three doses.
- 600 microgram was kept every 12^{th} 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 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
- Diarrhea
- Headache
- Excessive bleeding
- Abdominal cramps
- Dizziness

RESULTS AND ANALYSIS

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 test (Analysis of variance test)

TABLE I : AGE DISTRIBUTION

S.No	Age Group	Misoprostol 200 µg		Misoprostol 400 µg		Misprostol 600 µg	
		No. of Cases	%	No. of Cases	%	No. of Cases	%
1	<20	7	7	9	9	7	7
2	21-25	37	37	38	38	35	35
3	26-30	40	40	42	42	43	43
4	>30	16	16	11	11	15	15

- 78% of the patients were in the age group of 21 – 30 years.
- 14% were in the age group of 30 and above.
- Only less than 10% of the patients were in the age group of 16-20 years.

TABLE II: PARITY

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

- Unmarried pregnancies were only 2% in the three groups.
- Primigravida were about 15% in the three groups where as parous women were about 82%

TABLE III: SOCIO ECONOMIC STATUS

S.No	Socio – Economic Status	Misoprostol 200 µg		Misoprostol 400 µg		Misoprostol 600 µg	
		No. of Cases	%	No. of Cases	%	No. of Cases	%
1	Class I / II	0	0	2	2	4	4
2	Class III	12	12	13	13	10	10
3	Class IV /	88	88	85	85	86	86

	V						

- Above 86% of the women belonged to socioeconomic status class IV / V
- Only 3% of the women belonged to class I / II Socioeconomic status
- In class III socioeconomic status group there were about 12% of women.

TABLE IV : GESTATIONAL AGE

S.No	Gestational Age	Misoprostol 200 µg		Misoprostol 400 µg		Misoprostol 600 µg	
		No. of Cases	%	No. of Cases	%	No. of Cases	%
1	< 7 Weeks	10	10	6	6	8	8
2	7-9 Weeks	20	20	22	22	16	16
3	10-12 Weeks	70	70	72	72	76	76

- 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 belong to less than 7 weeks gestational age group

TABLE V: INDUCTION – ABORTION INTERVAL IN HOURS.

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

UMP – Unmarried pregnancies.

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

TABLE VI : COMPLETE ABORTION

S.No	Characters	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	%
01	Nullipara	10	10	3	3	9	9	2	2	4	4	2	2
02	Parous	38	38	8	8	31	31	6	6	15	15	5	5

- Complete abortion occurred in 41% of cases in 200 microgram group and in 52% of cases in 400 microgram group.

- Complete abortion was higher in 600 microgram group. It occurred in 74% of cases

TABLE VII: SIDE EFFECTS

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

- Symptoms were less with 200 microgram group.

- Vomiting was higher in 600 microgram group (41%), where as it was noted only in 27% of cases in microgram group.

- Only one case had diarrhea in 200 microgram group. 2% in 400 microgram group and 5% in 600 microgram group had diarrhea.

- Onset of abdominal / Uterine cramps and excessive bleeding were almost similar in all three groups.

- None of them in 200 microgram group had dizziness.

- Only 1% in 400 microgram group and 2% in 600 microgram group had dizziness

STATISTICAL ANALYSIS OF RESULTS

TABLE VIII: ANALYSIS OF INDUCTION – ABORTION INTERVAL IN HOURS

Dose in Microgram	N	Mean	Standard Deviation	Maximum Interval	Minimum Interval
200	41	22.22	.613	24	21
400	52	19.57	.936	22	18
600	74	16.59	2.024	21	14

N – No. of complete abortion.

- The mean induction- abortion interval in 200µg, 400µg and 600µg group is 22.22 hours, 19.57 hours and 16.59 hours respectively.

TABLE IX : ANALYSIS OF INDUCTION – ABORTION INTERVAL IN DIFFERENT MISOPROSTOL GROUPS

Misoprostol Groups	df	p value
Between Groups	2	0.000
Within Groups	164	0.000
Total	166	

df – Degrees of freedom.

- By ANOVA 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 **0.000**

TABLE X : ANALYSIS OF INDUCTION – ABORTION INTERVAL IN GESTATIONAL AGE GROUPS

Gestational Age Groups		df	p value
< 7 weeks	Between	2	0.027
7 – 9 Weeks	Groups		
10 – 12 weeks	Within Groups	164	0.027
	Total	166	

df – Degrees of freedom .

- By applying statistical analysis (ANOVA test), it is found that there is a significant difference in I-A interval between the three gestational age groups and within the groups and p value is **0.027**

TABLE XI: ANALYSIS OF INDUCTION – ABORTION INTERVAL IN PARITY

Parity		Mean	Standard Deviation	df	p value
UMP	Between	20.90	3.452	3	0.233
G1	Groups	18.61	3.232		
G2	Within	18.53	2.752	163	0.233
G3	Groups	19.16	2.541		
	Total			166	

UMP – Unmarried pregnancies

- Mean induction- abortion interval is 20.90, 18.61, 18.53 and 19.16 in unmarried pregnancy, primigravida, second gravidae and third gravidae respectively. By Statistical analysis of induction abortion interval, there is no significant difference between the parous and nulliparous groups, p value is **0.233**.

TABLE XII : ANALYSIS OF COMPLETE / INCOMPLETE ABORTION

S.No	Variable	Misoprostol 200 µg	Misoprostol 400µg	Misoprostol 600µg	p value
1.	Complete Abortion	41	52	74	0.01
2	Incomplete Abortion	48	40	19	0.05

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**

TABLE XIII: STATISTICAL ANALYSIS OF SIDE EFFECTS

Side Effects	Misoprostol	Misoprostol	Misoprostol	Total

	200 µg	400 µg	600 µg	
Symptom Free	7.8%	4.2%	4.8%	16.8%
Vomiting	6.0%	15.6%	20.4%	41.9%
Diarrhea	0.0%	0.6%	1.8%	2.4%
Abdominal \ Uterine Cramps	7.8%	6.0%	5.4%	19.2%
Excessive Bleeding	3.0%	4.2%	11.4%	18.6%
Dizziness	0.0%	0.6%	0.6%	1.2%
Total	24.6%	31.1%	44.3%	100.0%

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% diarrhea, 1.2% dizziness.

Among the three dosage groups, there is statistically significant difference in the incidence of side effects, vomiting [6.0%, 15.6%, 20.4%], diarrhea [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 600μg 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 were 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 microgram 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 microgram, 400 microgram and 600 microgram 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 microgram was used and 60% when the dose was 400 microgram

Success rate of 81% of complete abortion with 800µg [**Esteve** JL et al 1998] at 24 hours interval.

Success rate is 97% complete abortion using 800 microgram at 24 hours interval ***(Jain, Mekstroth, Lacarra 1998)***

84% of complete abortion occurred when 800 microgram was used at 24 hours interval by carbonell et al 2001.

Ngai et al showed success rate of 85% complete abortion using 800 microgram of misoprostol at 48 hours interval.

Table VII : In this study 27% of the women in the 200 µg group had vomiting. Other side effects reported were uterine/ abdominal cramps (18%),excessive bleeding (26%) and diarrhea (1%).

Study by *Bugalho et al*, reported nausea (19%), vomiting (6%), diarrhea (7%), fatigue (12%) and lower abdominal pain (71%).

In this study 400 µg group women experienced the following side effects viz., vomiting (35%), excessive

bleeding (25%) abdominal cramps (18%), diarrhea (2%) and Dizziness (1%)

When compared to other two groups 41% of women in 600 µg group experienced vomiting, 16% uterine cramps, 5% diarrhea and 2% dizziness.

Various studies conducted by *Carbonell et al* [1999 – 2000] using different doses at different intervals showed varying side effects.

Nausea (22%), vomiting (17%), diarrhea (54%), dizziness (25%), Headache (19%), fever (26%), pelvic pain (99%) experienced by women using 800µg misoprostol *(Carbonell , Fernandez C , et al* 1998.)

TABLE VIII : Mean induction - abortion interval in 200µg, 400µg and 600µg 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(24hours), when compared with oral route with a statistically significant difference of 0.01.

Study by F. Dong et al (BJOG) using 800µg 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.

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

TABLE X : Difference in I-A interval between the three gestational age groups is statistically significant and pvalue is **0.027.**

Surg Capt Sushil Kumar et al reported success rate of 67% using 800µg vaginal misoprostol at <8 weeks and 83% at 8 – 12 weeks.

TABLE XI : There is no statistically significant difference in I-A interval in parity and pvalue is **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 pretreatment 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), diarrhea (p=0.01) and unpleasant mouth taste (p=0.0001) in sublingual group compared with women in the vaginal route.

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 200µg misoprostol group with a statistically significant difference ($p < 0.05$)

SUMMARY

This present randomized 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.

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 analyzed.

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 were 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 microgram.
- Complete abortion varied in the three groups and was highest in 600 µg group (74%)
- Side effects were less in women who received 200µg. None of the women in this group had dizziness and only one patient had diarrhea. Incidence of bleeding was similar in all the three groups.
- Mean I-A interval using 200µg was 22.22 hours, with 400µg it was 19.57 hours and with 600µg 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 with in 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 200 µg.
- 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 set up with facilities for further management as and when required will go a long way in reducing the unwanted interferences by unscrupulous persons.

BIBLIOGRAPHY

1. Ayres-de-Compos D, Teixiera-da-Silva J, Compos I, Patricio B (2000). Vaginal misoprostol in the management of first-trimester missed abortions. Int J Gynaecol Obstet Oct: 71(1):53-7

2. Bugalho A, Bique C, Almeida L, Bergstrom S (1993). Pregnancy interruption by vaginal misoprotol. Gynecol Obstet Invest; 36(4):226-9.

3. Carbonell JL, Varela L, Velazco A, Fernandez C (1997a). The use of misoprostol for abortion at < or =9 weeks gestation. Eur J Contraception Reprod Health Care Sept; 2(3) : 181-5

4. Carbonell JL, Varela L, Velazco A, Fernandez C (1997b). The use of misoprostol for termination of early pregnancy. Contraception 55(3):165-8

5. Carbonell JL, Varela JL, Varela L, Velazco A, Cabezas E, Tanda R, Sanchez C (1998). Vaginal misoprotol for late first trimester abortion. Contraception May; 57(5): 329-33.

6. Carbonell JL, Varela L, Velazco A Tanda R, Sanchez C (1998). Vaginal misoprostol for early second [illegible] ion. Eur J Contracept Reprod Health Care: 3(2): 93-8

7. Carbonell JL, Varela L, Velazco A, Tanda R, Sanchez C (1999). Vaginal misoprostol for abortion at 10-13 weeks' gestation. Eur J Contracept Reprod Health Care; 4(1): 35-40.

8. Carbonell JL, Varela L, Velazco A, Tanda R, Barambio S, Chami S (2000). Vaginal misoprostol 600mcg for early abortion. Eur J Contracept Reprod Health Care; 5(1): 46-51.

9. Carbonell JL, Rodriquez J, Argon S, Velazco A, Tanda R, Sanchez C, Barambio S, Chami S, Valero F (2001 a). Vaginal misoprotol 1000 microg for early abortion. Contraception Mar;63(3):131-6

10. Carbonell JL, Velazco A, Varela L et al (2001 b). Misoprostol for abortion at 9 – 12 weeks' gestation in adolescents. Eur J Contracept Reprod Health Care; 6(1): 39-45.

11. Gonzalez CJ, Marques Dias MJ, Kim CA, Sugayama SMM, Paz JA Da, Huson SM, Holmes LB (199[illegible] [illegible]tal abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. The Lancet Volume 351, Issue 9116, 30 May, 1624 -1627.

12. Faundes A, Santos LC, Carvalho M, Gras C (1996). Post-abortion complication of pregnancy with misoprostol Adv Contracept Mar;12(1)1-9.

13. Haberal A, Celikkanat H, Batioglu S (1996). Oral misoprostol use in early complicated pregnancy. Adv Contracept Jun; 12(2):139-43

14. El-Refaey H, O' Brien P, Morafa W, Walder J, Rodeck C (1997). Use of oral misoprostol in the prevention of postpartum haemorrhage. Br. J Obstet Gynaecol. Mar; 104(3):336-9.

15. Winikoff B, Ellertson C, Clarke S, Analysis of failure in medical abortion. Contraception 1996;54:323-327

16. Blanchard K, Winikoff B, Ellertson C, Misoprostol use alone for termination of early pregnancy: a review of the evidence.

17. Bugalho A, Faundes A, Jamissa J, Usfa M, Maria E, Bique C. Evaluation of the effectiveness of vaginal misoprostol to induce first trimester abortion.

18. Crenin MD, Vittinghoff E. Methotrexate and misoprostol vs. misoprostol alone for early abortion: a randomized controlled trial. Journal of the American Medical Association 1994;272:1190-1195.

19. Jain JK, Mishell DR, Mekstroth K, Lacarra M. The use of vaginal misoprostol for termination of pregnancies <56 days [abstract]. American Public Health Association 126th Annual Meeting, Washington, D.C. November 15-18,1998

20. Koopersmith TB and Mishell DR. The use of misoprostol for termination of early pregnancy. Contraception 1996;53:237-242.

21. Ngai SW, Tang OS, Chan YM, Ho PC. Vaginal misoprostol alone for medical abortion up to 9 weeks of gestation: efficacy and acceptability. Human Reproduction 2000;15(5):1159-1162.

22. Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostal and mifepristone. Lancet 1991;338:1233-1236

23. Tang OS, Miao BY, Le SW, Ho PC. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: efficacy and acceptability. Hum Reprod 2002; 17:654-8.

24. Government of India ,Mnistry of Health and Family welfare Annual repor 2003 -2004.

25. Ashok PW. Hamoda H, Nathani F, Flett GM, Templeton A. Randomised controlled study comparing oral and vaginal misoprostol for cervical priming prior to surgical termination or pregnancy. BJOG.2003 Dec;110(12):1057-61

26. E.Ekerhovd, MD, PhD, N.Radulovic, MD and A. Norstrom, MD, PhD. Gemeprost Versus Misoprostol for cervical priming before first – trimester abortion: A randomized controlled trial. Obstetrics & Gynecology 2003;101:722-725.

27. Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998;338:1241-7.

28. Peyron R, Aubeny E, Targosz V, Silvestre L, Renault M, Elkik F, et al. Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. N Engl J Med 1993;328:1509-13.

29. Schaff EA, Fielding SL, Eisinger SH, Stadalius LS, Fuller L. Low-dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days. Contraception 2000;61:41-6.

30. Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. Obstet Gynecol 2002;99(5 pt 1):813-9.

31. Kruse B, Poppema S, Creinin MD, Paul M. Management of side effects and complications in medical abortion. Am J Obstet Gynecol 2000;183(2 suppl): S65-75.

32. Tang OS, Wong KS , Tang LCH, Ho PC. (1999) Pilot study on the use of repeated doses of misoprostol in termination of pregnancy at less than 8 weeks of gestation. Advances in Contraception, 15, 211-6

33. Billings DL. Misoprostol alone for early medical abortion in a Latin American clinic setting. *Reprod Health Matters.* Nov 2004;12(24 Suppl):57-64.

34. Blanchard K, Shochet T, Coyajı K, Ini Nhu Ngoc N, Winikoff B. Misoprostol alone for early abortion: an evaluation of seven potential regimens. *Contraception.* Aug 2005;72(2):91-97.

35. Ekmekcioglu,Demirci,Yilmaz and Tatli (1998).Intrauretheral misoprostol a different agent in the treatement of erectile dysfunction. Sexual dysfunction 1:161.D01:10.1046/J.1460-2679.1998.

36. Barbosa,RM (1993).The Brazilian experience with cytotec. Stud Fam plan 24(4); 236-40. PMID 8212093.

37. Kuldip singh, Y.F.Fong, F.Dong.BJOG.An international journal of Obstetrics and Gynecology. Volume 110 page 175- Feb 2003.

PRO_ _ _ _IA

COMPARATIVE STUDY OF EFFICACY OF THREE REGIMENS OF VAGINAL MISOPROSTOL IN THE FIRST TRIMESTER TERMINATION OF PREGNANCY

NAME : AGE: A NO:

ADDRESS DOA: HEIGHT

DOD: WEIGHT

OCCUPATION:

SOCIO ECONOMIC CLASS:

MENSTRUAL HISTORY:

LMP REGULAR / IRREGULAR

MARITAL HISTORY:

MARRIED SINCE

UNMARRIED

OBSTETRIC FORMULA: G P L A

H/O PREVIOUS MTP DONE:

1. HOW MANY WEEKS
2. METHOD ADOPTED

H/O PREVIOUS SURGERY: IF ANY:

REASONS FOR MTP:

- SOCIAL CAUSE

- FAILURE OF CONTRACEPTION
- UNWED PREGNANCY
- MEDICAL REASONS

PAST MEDICAL / SURGICAL HISTORY

H/O DIABETES HYPERTENSION / PULMANORY TUBERCULOSIS / BRONCHIAL ASTHMA / EPILEPSY / HEART DISEASE / ENDOCRINE DISORDER / ALERGY TO DRUG.

ON EXAMINATION:

GENERAL

ANAEMIA	YES / NO
FEBRILE	YES / N O
PEDAL EDEMA	YES / NO
TEMP	PR
BP	CVS
RR	RS.

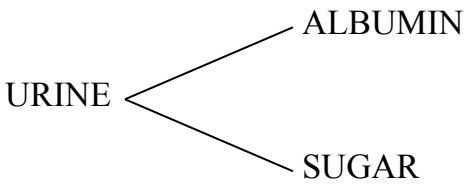
ABDOMINAL AND PELVIC EXAMINATION:

PER ABDOMEN EXAMINATION:

LOCAL EXAMINATION:

BIMANUAL PELVIC EXAMINATION:

INVESTIGATIONS



Hb%

BLOOD GROUP / Rh TYPING: (IN PRIMI)

HIV (WITH CONSENT):

VDRL:

USG (wherever indicated)

DATE / TIME OF ADMINISTRATION OF VAGINAL, MISOPROSTOL (200 µg, 400 µg, 600 µg)

TIME OF EXPULSION: COMPLETE / IN COMPLETE:

IF INCOMPLETE ADDITIONAL METHOD USED FOR COMPLETING THE ABORTION:

COMPLICATIONS:

1. VOMITING
2. DIARRHEA
3. EXCESSIVE BLEEDING
4. DIZZINESS
5. ABDOMINAL PAIN / UTERINE CRAMPS

TOTAL INDUCTION ABORTION INTERVAL