AIM OF STUDY
AIMS AND OBJECTIVES

The present study is designed:

1. To evaluate the efficacy, safety and tolerance of intra-vaginal misoprostol compared to the traditional use of intra-cervical dinoprostone in mid-trimester abortion.

2. To formulate a standard dosage schedule for mid-trimester abortions using misoprostol intra-vaginally.

3. To evaluate the side effects of misoprostol (intra-vaginal) compared to dinoprostone (intra-cervical) in the usual abortifacient dosages as used in mid-trimester abortions.

4. To study the population coming for mid trimester abortion as regards to age, parity, socioeconomic status, literacy, gestational age and various other parameters.
REVIEW OF LITERATURE
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**Historical review**

According to the need of society, laws are usually made to change. Before the change of abortion law (April 1971), there were people who considered it highly immoral to think or talk about abortion, while others felt immense need for liberalization of law for inducing abortions.

Since the beginning of this century, the court and non-government authorities have made efforts of lowering the birth rate. This control of child bearing can be achieved by sterilization and other contraceptive devices. Medical termination of pregnancy also plays important role in curbing the flood of population.

Induction of abortion, either to safeguard the life of a pregnant woman or as a method of limiting the family was practiced by human society since ancient times. When where and by whom was it performed first will never be known.

Various techniques of inducing abortion have been reported. Strong poisons were recommended 5000 years ago in an ancient Chinese manuscript written by emperor Shen Nung.

Others suggested strenuous exercises, application of hot ashes to the belly and application of different herbs as well. Among primitive people, almost every tribe had some method of abortion.
Eber's Papyrus discussed method of inducing abortions. Abortifacient elements were dates, onions, and fruits of acanthus or honey, which had to be applied over the vulva.

Greeks had knowledge of both spontaneous as well as induced abortion. Plato (427-347 BC) recommended obligatory abortion for every woman who conceived after the age of 40 Years. It was also advocated by Aristotle for a woman who already had the prescribed number of children, but it had to be done only before quickening.

In about 130 A.D., Sonarus probably the greatest obstetrician and gynaecologist of Rome of Mat era, wrote a text on diseases of women in which he commented that it was easier to induce abortion in 3rd month but that endometritis and convulsions (tetanic) may occur as complications.

In 13th century, English jurist Breaton framed rules of the common law that killing the foetus after quickening was murder and before quickening it was crime. It was in 1929 that the Great Britain legalized abortion when mother's life was endangered. During last 50 years there has been changes performed in abortion laws in various countries of the world.

Abortion in India

The increased mortality and morbidity due to the illegal abortion was a matter of concern to everybody in medical field. MTP was legalized in India with two main reasons in mind. Firstly, as a population control measure as population control could not be achieved satisfactorily by the various contraceptive methods either due to individual's method failure or due to non-adoption by the ignorant and uneducated masses.
The second objective was to transfer large number of criminal abortions with all their complications from the untrained quacks, to the safe hands of skilled and specialized gynaecologist.

Gynaecologist entrusted with this responsibility looked at the problem with four aspects-
1. The method employed should be safe for mother.
2. The technique used should be easy.
3. The procedure should not involve prolonged hospital stay, thereby accelerating rate of turnover per bed.
4. Lastly, the method should be cheap.

The method of termination of pregnancy from 12th week onwards is a problem of obstetricians even today. The chief aim is physiological delivery of the foetus with safety to the mother.

Various methods tried for mid-trimester abortion are –

A. Surgical abortion:
1. Dilation and Evacuation

In USA and in non-NHS sector in UK, dilatation and evacuation is considered as preferred method for termination of second trimester pregnancy. This method is faster, carries no risk of live birth, is more compassionate in terms of women and can be performed on a outpatient basis. A greater degree of skill is required to perform this procedure, a safe and effective method only in the hands of those who are trained and skilled in the technique. Serious complications like cervical laceration, uterine perforation and bowel injury are a distinct possibility even in the hands of expert. Although D/E is reported to be the safest method of second trimester abortion, beyond 16 weeks this procedure is taught infrequently (Auntry, AM et al, 2002).
2. Aspirotomy

This is a combination of vacuum aspiration of liquor followed by embryotomy and removal of the products of conception under paracervical block. Although not a mandatory prerequisite, this procedure can be better performed under ultrasound guidance. In spite of the claim of almost similar results and complications like D/E, the method never became popular, possibly because of significantly high incidence of anticipated complications and the need for development of expertise and skill in the procedure.

3. Hysterotomy

Effective non-surgical methods have made surgical procedures, particularly the traditional hysterotomy almost obsolete and largely discredited. Now the only role of hysterotomy is in rare cases of failure following induction of abortion.

B. Medical Abortion

Medical abortion is ideally an attempt to stimulate uterine contraction and initiate cervical dilatation with an aim of complete expulsion of products of conception so as to mimic a mini-labour. Considering the increased incidence and severity of complications associated with surgical methods of termination and the relative lack of adequate trained personnel for second trimester termination of pregnancy by dilatation and evacuation, the need for an alternative and safe method was more importantly felt than ever. The scope of training for development of skill, the technique of dilatation and evacuation, amongst the junior residents is gradually becoming far from reality and is now regarded as a lost art. When morphometric evaluation of the foetus is required, as in cases of second trimester termination due to genetic abnormality, medical abortion is a better option. Moreover, the protocol for medical abortion does not require
any special training and can be easily performed by the junior residents in a hospital with appropriate infra-structural back up.

1. Cervical tents

Tents enjoyed a long history of varying popularity. It decreases cervical resistance to forceful dilatation. Cervical ripening prior to surgical termination of pregnancy allows a greater cervical dilatation to be safely, effectively and confidently achieved thereby minimizing the complications.

The classical tents (laminaria) were derived from natural materials. Synthetic tents like Dilapan and Lamicel are also now available. Laminaria should be left in situ for 4-12 hours, lamicel for 4 hours and dilapan for 2-4 hours. Exceeding these limits achieves no further dilatation and the risk of sepsis, dumb swelling and entrapment increases.

Although never considered as a primary agent, tents are useful adjuncts to other methods for termination of second trimester pregnancy. The insertion of laminaria tent requires trained personnel. In addition to potential complications such as intrauterine displacement and perforation of the cervix, tents also cause discomfort to the patient.

2. Balloon Insertion

Introducing the foley’s catheter through the cervix, inflating the balloon with 30cc sterile saline and finally pulling the catheter downward until the balloon is engaged by the cervical internal os is an inexpensive and effective way of second trimester termination of pregnancy. Oxytocin augmentation was used with the expulsion of catheter or with the initiation of uterine contraction, when necessary.
The procedure is considered as failure when there is no effective uterine contraction or cervical dilatation within 48 hours. The main drawback of the balloon insertion is the discomfort caused by the strapping of the catheter to the patients inner thigh firmly that provides traction to the cervix.

3. **Intra Amniotic Hypertonic Saline**

For procuring second trimester termination, intra-amniotic instillation of hypertonic saline (20%) was extensively used in Japan from 1946 to 1952. The results were satisfactory with an average induction-abortion interval of 32 hours and a success rate of almost 80% within 48 hours. However, the complication rates were also high, the commonest being haemorrhage due to incomplete abortion and infection. The other noted complications were cervical tear, hypernatremia (rarely severe), and necrosis of myometrium and rarely coagulopathy. More importantly, the unacceptably high maternal mortality has ultimately become responsible for its gradual decline in use.

4. **Ethacridine Lactate**

Ethacridine lactate was first used by Miranov in Russia in 1950 for second trimester pregnancy termination. Trans-cervical extra-ovular instillation of this acridine dye was found to be an inexpensive, safe and effective method by various authors. Extramniotic route was found to be more effective as compared to intra-amniotic route. Administration of various abortifacients through extra-amniotic route dates back to 1846, although Manabe popularized it. This route is devoid of the complications associated with intra-amniotic route and can safely and effectively be employed between 12-14 weeks of pregnancy (so called grey zone of pregnancy). The drawback of this method has been reported to be the
long induction-abortion interval (23-42 hours) and the need for augmentation with oxytocin in majority of cases. However, simultaneous use of different drugs or devices having synergistic effect on uterine stimulation may reduce induction abortion interval and also increase success rate-

5. Urea

Intra-amniotic instillation of 150-200 ml of 40-60% Urea, an inert substance, has been observed to be effective in procuring second trimester termination. As compared to hypertonic saline urea is less toxic to maternal tissue. The success rate is also lower than hypertonic saline. However, addition of adjuvants like intra-amniotic PGF$_2$\alpha or introduction of intra-cervical tents helps to improve the success rate.

6. Oxytocin

Caldeyro Barcia et al found that the oxytocin dose required to produce 120 montevideo units of uterine activity is eight-fold higher at 20 weeks of gestation than at 38 weeks. This weak uterine response to oxytocin at early weeks of gestation is the greatest obstacle of using oxytocin infusion for achieving second trimester termination of pregnancy. Clinical and biochemical observations suggest that a concentrated oxytocin infusion protocol may be effective. Highly concentrated oxytocin solution (300 IU / 500 cc oxytocin over three hours) may lead to water intoxication. However, standard oxytocin infusion protocol is commonly used as an adjunctive to other protocol with an aim to reduce the induction-abortion interval and also to increase the chance of completeness of abortion.
Newer drugs in use

7. Mifepristone

Progestosterone is central to the maintenance of pregnancy and is thus the ideal target for fertility regulation. Mifepristone, a receptor blocker, is usually given as pre-treatment, prior to prostaglandin administration in mid-trimester termination of pregnancy.

Pre-treatment with mifepristone required significantly fewer gemeprost pessaries to induce abortion and experienced significantly less pain than the women who received placebo and this combined regimen is also associated with fewer gastrointestinal side effects (Rodger MW et al, 1990) pre-treatment with oral mifepristone (100mg daily for two days) optimizes the outcome of vaginal misoprostol for mid-trimester termination, (Cheng L et al, 1999).

The combination of oral mifepristone 200 mg single dose followed by vaginally and orally administered misoprostol provides noninvasive and effective regimen for second trimester termination of pregnancy (Ashok PW et al, 1999).

8. Trilostane

Trilostane is a 3α-hydroxysteroid dehydrogenase inhibitor, which reduces progesterone production from its precursor pregnenolone. As a pretreatment, prior to misoprostol administration trilostane, was evaluated in second trimester termination. Trilostane is an effected pretreatment agent by reducing the induction to abortion interval in mid trimester termination (Roux PA et al, 2002).

9. Prostaglandins

The uterine stimulation and cervical ripening property of the prostaglandins was successfully utilized for termination of second
trimester pregnancy since last four decades. All possible routes were tried-intravenous, intramuscular, intra-amniotic, extra-amniotic and vaginal.

Currently used products are analogous of PGE$_1$ (gemeprost, misoprostol).

a **Dinoprostone** (PGE$_2$ gel) is also an effective method of cervical ripening when used intra cervically. But retained placenta in 2% was a major complication and also has severe gastrointestinal side effects.

b **Gemeprost** is available as vaginal pessary (1mg). Intravaginal route is used and repeated at a varying interval of three to six hours. Gemeprost can be used synergistically with pre treatment with miferpristone.

c **Misoprostol** synthetic PGE, analgesic initiates cervical dilatation and stimulates an increase in intensity and frequency of uterine contraction. It discussed in detail later on.

**Prostaglandins**

Prostaglandins are naturally occurring compounds found in body secretions and are readily released.

**Historical survey**

Prostaglandins were first discovered in seminal fluid by Kurzrok and Liebin (1930), who noted that human uterus undergoes strong uterine contractions on instillation of fresh human semen.
Von Euler coined the name prostaglandin in 1935, as it was thought to be secreted from the prostate but it was misnomer as it was the secretion which has been isolated by Bergstone and Sjovall in crystalline form from the sheep's seminal vesicle. The compound was not paid much attention until the II\textsuperscript{nd} world war.

Prostaglandins were used for the first time in 1963 by Karim and associates for induction of abortion. Since then a large number of trials have been carried out in many countries on induction of labour and abortion. Prostaglandins have been found to be very effective at any stage of pregnancy, so it is found to be very useful for missed abortion, intrauterine deaths and hydatiform mole (Roth Bkandel and Karim Filsh, 1970).

Prostaglandins are effective in first as well as in IIInd trimester abortion. Various routes have been tried to evaluate the efficacy and to lower the side effects. First of all, intravenous PGF\textsubscript{2\alpha} infusion was tried. This route was associated with unacceptable side effects like hypotension, nausea, vomiting and thrombophlebitis.

Next intrauterine route was tried, with the aim to localize the site of action and reduce the systemic side intra-amniotic routes were tried with high efficacy and less side effects but required intra-uterine manipulation and repeated administration involved potential risk of sepsis. To get rid of intra-uterine manipulation, PGF\textsubscript{2} was tried by intra-muscular and intra-vaginal routes.

**Distribution of prostaglandins in human reproductive organs and fluid**

Recent and more definite studies have shown that the distribution of prostaglandins is not restricted to male accessory
glands or their secretions as reported earlier, but prostaglandins have universal distribution in the female reproductive organs and fluid also. With increasing and ongoing researches, evidence has accumulated that prostaglandins are active throughout the reproductive system.

By the late 1970’s, prostaglandins were known to be involved in hypothalamic and pituitary hormone release, ovulation, development of corpus luteum, uterine contractions in labour, spontaneous abortion ejaculations and sperm transport.

**Location, structure and purification**

The isolation of prostaglandin E₂ and F₂α in pure crystalline form from the sheep vesicular gland was reported in 1957 by Berstrom and Sjovall. With the elucidation of the structure of primary prostaglandin and the total synthesis by E.J. Corey et al. Haward (1969) and UP John company, became universal. The ultramicro analysis proved that they were unsaturated hydroxy fatty acid has empirical formula C₂₀H₃₄O₅ and C₂₀H₃₆O₅ respectively. 13 different compounds were isolated, all derivative of parent substance prostanoic acid containing 20 carbon atoms.

Prostaglandin are divided into five types based upon the chemical functioning in the ring structure called cyclopentane and two side chains and are named as F,E,A,B and C.

**Structure**

![Prostanoic acid structure](image_url)
Prostaglandins are again grouped into mono, bis or tri unsaturated classes according to the number of carbon to carbon double bonds in the side chains which is sited as 1,2,3 in the subscripts e.g. PGF₁, PGF₂ and PGF₃. They are divided into stereo isomer and are substituted alpha or beta e.g. PGF₂ alpha.

The extracts of sheep seminal vesicle yield very little amount of prostaglandin and was very expensive, so chemical synthesis by E.J. Corey has provided very inexpensive prostaglandins in large amounts.

**Occurrence**

Prostaglandins are found in all mammalian tissues & body fluids e.g. seminal fluid, lungs, kidney, brain and reproductive system (Anderson, 1974). The concentration of prostaglandins is 100 µg/ml in seminal fluid, while in other tissue it is less than 11 µg/gm.

**Biosynthesis and Metabolism**

The complex enzymic system which takes part in synthesis of prostaglandins is present in every mammalian tissue. Capability of synthesis is different in different tissue e.g. in seminal vesicle it is 75%, 10-20% in lungs and kidney, 3% in gut and less than 1% in spleen and aorta. They are synthesized from essential fatty acids. Among them arachidonic fatty acid is the most important. First step in the bio conversion of arachidonic acid to prostaglandins (PGF₂ and PGF₂α), prostacyclins (PGI₂) and thromboxane (TαA₂) is the formation of cyclic endoperoxides, prostaglandin G and H. The enzyme responsible for the conversion of AA to PGH₂ is known as fatty acid cyclo-oxygenase or prostaglandin edoperoxide synthetase or PGH synthetase.
NSAIDS like aspirin and indomethacin can inhibit the action of cyclo-oxygenase thereby inhabiting the formation of prostaglandins. Depending on the tissue, the endoperoxidases are further converted non-enzymatically into PGE$_2$, PGF$_2$$\alpha$, PGI$_2$ and TXA$_2$ (Sammelsson et al. 1975; Sammelsson et al. 1978). These conversions are extremely rapid and once the biosynthesis is initiated, it is completed within the few minutes in invitro system (Hamberg et al. 1975, Christensen and Green 1983).

Structure

Arachidonic acid

![Arachidonic acid structure](image)

Metabolism

Natural prostaglandins are metabolized rapidly by beta-oxidation which is the major route and also by dehydrogenases. The enzymes involved in the initial conversion are found in the lungs, liver and kidney (Auggard, Larsson and Sammelsson, 1971).

After intravenous administration of PGF$_2$, the drug disappear very rapidly during the first ten minutes then reaches a steady low level in first hour, excreted completely in ten hours. Total recovery is 60% by excretion i.e. 40% from the urine and 20% from the urine.
Physiology and pharmacology

Prostaglandins cause contraction of all smooth muscles. Response could be modified with change of ionic composition of medium, hormones and blocking agents.

Mechanism of action

The mechanism seems to be by oxidative metabolism. Probably it causes membrane depolarization and release of bound calcium. Action of PGE and PGF alpha are quantitatively similar but different receptors may be involved.

Parturition: Although a controversy still exists about the factors responsible for the initiation of labour, the fact that the prostaglandins are involved in the physiology of labour as well as in the patho-physiology of spontaneous abortion and premature abortion and premature labour is based on the following observation made by various workers.

- Stimulatory effect of prostaglandins on the pregnant uterus.
- Cervical priming.
- Raised levels of prostaglandins and their amniotic fluid during labour and spontaneous abortion.
- Inhibitory effects of prostaglandin antagonist and synthetase inhibitors on the uterine contractions.

Effect on human uterus:

Non pregnant uterus

In vitro studies: The PGE compounds generally inhibits, while PGF compounds stimulate the non-pregnant myometrium. The sensitivity is more to E compounds at ovulation, while to F compound, it is more at premenstrual period.
Non pregnant cervix

PGF2 causes marked relaxation, while F2 alpha results are unpredictable inhibition, contraction as well as no effect has been seen.

Pregnant uterus

The stimulatory effect of naturally occurring prostaglandins on the human myometrial strips obtained from one of the uterus in first and second trimester of pregnancy was first demonstrated by Bygdeman, 1964. PGF compounds are always stimulatory during pregnancy and sensitivity of myometrium is much higher than non pregnant.

In Vivo studies

The effect of PGE and PGF on pregnant uterus is always stimulatory (Roth Brandal et al, 1970; Bygdeman et al, 1970 and Karim 1971).

The sensitivity increases as term approaches. The stimulatory action is seen by different routes like intravenous, intramuscular, oral, vaginal, intrauterine (extra and intra amniotic).

However, the stimulatory response observed with the intra-amniotic PGF2 alpha was found to be different from the response obtained with intra-amniotic 15 (S) 15 methyl PGF₂ alpha (Wilquist et al. 73). He summarized the stimulatory effect with an analogue as slower to develop, reaching maximum after 4-hours but subsequently maintained at this level throughout the 24 hours of observation. In comparison, the intra amniotic injection of PGF₂ α caused a rapid uterine response which reached a maximum within 2-3 hours and then ablated progressively. The exact mechanism of action is still not
known. According to Carsten (1972), there are many PG receptors on the sarcoplasmic reticulum of the myometrium (intracellular membrane), which are responsible for conducting the signals to the myometrial fibres to contract and for initiating the contraction itself. PGE$_2$ and PGF$_2$ alpha cause the membrane to release the bound calcium into the cell fluid, these calcium ions in turn trigger off the contraction of the muscle fibres. The other possibility is that it acts indirectly through the release of oxytocin. Givenspie et al. 1972; have shown an increase of oxytocin levels in prostaglandin induced labour, and initiated that the increase is due to direct effect of prostaglandin on the pituitary. Caspo and Pulkkinen (1979) have suggested that the constriction of uterine and placental blood vessels is the first event which leads to the reduction in prostaglandin supply, thus making the myometrium receptive to prostaglandins.

**Effect on Pregnant Cervix in vivo**

The second major action of prostaglandin is on the cervix. It softens and dilates the cervix, commonly referred to as cervical priming or ripening. Prostaglandins, particularly PGE$_2$ that especially alter the structure of the connective tissue of the cervix and make it soft and dilated.

**Prostaglandins in maternal circulation and amniotic fluid**

Karim in 1986 demonstrated an increase in concentration during labour. The peak of PGF2 alpha was observed in the plasma 15 to 45 seconds after the peak of uterine contraction (Sharma et al, 1973) he reported a significantly higher concentration of PGF2 alpha in the umbilical vein of babies born vaginally as compared to those delivered by elective caesarean section.
Amniotic fluid is another resource from where a high concentration of prostaglandins have been reported during labour by many workers. Karim (1966) and Devlin (1967) were first to identify PGF2 alpha in amniotic fluid, during pregnancy and labour, and found it in higher concentration at the time of active labour. This rise in amniotic PGF2 alpha level during labour was not confined to the full term pregnancy but was observed during spontaneous abortion also. (Karim and Hiller, 1970).

**Inhibitory effect of prostaglandin antagonist and synthesis inhibitors on uterine contractions**

The satisfactory inhibition of uterine contraction with a prostaglandin antagonist or inhibitors of their synthesis, in the case of prostaglandins are involved in the physiology of labour.

The use of Ethyl alcohol to inhibit uterine activity in women with threatened abortion and premature labour was demonstrated by Fuchs et al (1957). The same authors showed that the administration of ethyl alcohol does not affect the uterine activity induced by oxytocin. Lewis and Schulman (1973) reported that aspirin (an inhibitor of prostaglandin synthesis) treatment in normal human pregnancy prolongs gestation and increases the duration of labour.

**Lactation and prostaglandins**

The physiological and pharmacological involvement of prostaglandin in lactation is not clear. The response of the human mammary tissue to prostaglandin was first studied by Cobo et al in 1974. They observed milk ejection property, both with PGF2 alpha when administered by single intravenous injection as with the equiactive amount of oxytocin. However, a latent period of 30-90 seconds was noted with PGF2 alpha before the response and the same
was two to four times greater than that of oxytocin. The exact mechanism of action of prostaglandin in increasing mammary pressure is not clear. Probably the prostaglandin acts indirectly either by oxytocin release or due to a metabolite of prostaglandin. The latent period observed in their study favours the oxytocin release theory while the long duration goes in favour of the metabolite theory.

Indirect evidence for the involvement of prostaglandin in lactation was shown by Shearman et al. (1972) who showed that almost all the patients experienced lactation after the intra-amniotic or extra-amniotic injection of prostaglandin for the termination of second trimester pregnancy.

Nasi et al. (1979) have reported inhibition of lactation by oral tablets of PGF₂ the physiological mechanism involved in the inhibition of lactation is not known.

**Fallopian tubes**

PGE causes relaxation of tube while PGF₂ contracted all parts of the tube.

**Ovary**

In animals prostaglandin acts as leuteolytic factor causing regression of corpus luteum and onset of menstruation regularly. In human beings prostaglandins have no effect on corpus luteum (Karim 75, Anderson 74, Duchhoelter et al. 78).

**Menstruation**

Endometrium produces both PGE and PGF₂ alpha and their level rise during luteal phase. These are also responsible for endometrial shedding, vomiting and pain in lower abdomen during menstruation.
Endogenous prostaglandin production decreases if progesterone, aspirin or indomethacin were given. (Helbert 1970 Juvier, 1974).

**Clinical application of Prostaglandins in obstetrics**

1. **Prostaglandins as abortifacient**

   Prostaglandins were first used for induction of labour in 1968. it was based on the fact that prostaglandin levels were such to be increased in maternal blood and amniotic fluid during labour and during cervical dilatation in cases of abortion. The abortifacient activity of prostaglandin is based upon the fact that it stimulates uterus at any gestational age.

   The various hypothesis are:

   i. **Direct myometrial stimulation**: Prostaglandin cause contraction and relaxation of uterus, due to increasing contraction of uterus, conceptus gets dislodged and results in abortion (Bergstrom et al 1971).

   ii. **Effect on foeto-placental unit**: This is most widely accepted theory by Coceani et al 1972. According to this theory prostaglandin first induces uterine contraction. Sustained uterine contraction causes decreased blood supply to placenta and throphoblast. This reduction in uterine blood flow causes suppression of foeto-placental endocrine function i.e. HCG levels become low. This in turn reduces corpus luteum activity and decreases progesterone levels. It has double fold effect. It reduces myometrial threshold for contractility and also results in increased endogenous prostaglandin synthesis. The overall effect is increased cyclic uterine activity, which results in abortion (Canter et al, 1971).
2. Use of Prostaglandin in abnormal pregnancy: Various investigators have used prostaglandins for the termination of missed abortion, hydatiform mole, intrauterine foetal death and anencephalic pregnancy.

3. Induction of labour: Prostaglandins are being used extensively in induction or augmentation of labour either spontaneous labour or induced.

4. Post partum haemorrhage: Prostaglandins have been found to be effective in controlling postpartum uterine haemorrhage when administered by different routes. Local administration directly into the uterine musculature trans abdominally or transvaginally, resulted in the dramatic reduction in rate of bleeding (Takagi et al, 1976; George et al, 1983).

5. Dysmenorrhoea and other uterine pathology: From the result of the studies one may conclude that prostaglandin is one of the causative factors. In the aetiology of primary dysmenorrhoea, Pickles & Hall (1963) demonstrated a higher than normal amount of PGF2α in the menstrual fluid of dysmenoerhic women. These levels were reduced after aspirin and indomethacin administration.

6. Intra uterine contraceptive devices: The possibility of involvement of prostaglandin in the anti-fertility action if IUCD is evaluated by some investigators.

7. Preoperative cervical dilatation: The use of prostaglandin analogues for the dilatation of the cervix gives a better success rate than the usage of tents or other procedures.
Side effects

Prostaglandins have numerous side effects but none of them is life threatening and they disappear very rapidly on withdrawing the drug. These side effects are due to action of prostaglandins on various tissues of the body.

1. **Gastro-intestinal tract**: Vomiting, diarrhoea and abdominal pain are the most common side effects with prostaglandins. The cause of diarrhoea is enteropooling i.e. accumulation of fluid in small bowel, the cause of this pooling is:
   - Inhibition of reaabsorption of fluid from intestinal lumen by prostaglandins.
   - Out pouring of fluid from blood into lumen.

   The degree of enteropooling is dependent upon the dose of prostaglandin. The fluid then moves into large intestine and gets mixed with normally formed stools which are expelled out. Thus action is just like Cholera exotoxin (Robert et al, 1976). Lomitol controls diarrhea partially and loperamide has slightly higher therapeutic value. it acts by inhibiting peristalsis by interfering with cholinergic and non-cholinergic mechanism.

   Vomiting is due to local effect on intestine and can be controlled by prochlorperazine. Abdominal pain is due to contraction of intestinal muscles. Prostaglandins of F series have more Git side effects.

2. **Uterine pain**: The cause of uterine pain is rise in uterine tonus, the base line tonus becomes 20-25 mmHg which gives rise to continuous pain. Pethidine is presumed to be effective analgesic
for this, without interfering with the abortifacient activity, but is rarely required.

3. **Fever**: The cause of fever is action on temperature regulating mechanism probably at hypothalamic level, the temperature comes down after abortion. PGE series have more specific pyrexial action than PGF series.

4. **Respiratory side effects**: Prostaglandins sometimes produce bronchospasm, dyspnoea and respiratory difficulty. The cause is stimulation of respiratory smooth muscles. PGF series have been found to be vasoconstrictors (Zurier et al, 1974) while PGE series has vasodilator action. So, PGF series give rise to respiratory difficulty on I.V. infusion while PGE series may be used to cure the asthmatic patients (Zurier et al, 1974).

5. **Cardiovascular side effects**: Fishburn et al. (1972) has reported no change in cardiac output, heart rate or central venous pressure even with large doses of PGF$_2$ alpha by I.V. infusion. Lee et al, (1974) has reported that PGF$_2$ infuses causes fall in blood pressure especially in diastolic blood pressure. With large intravenous infusion flushing of face, headache, flashes of light, dizziness etc have been reported which are due to relaxant effect of prostaglandin on vascular smooth muscle.

6. **Effect on blood coagulability**: Prostaglandin cause a decrease in haematocrit value but all other factors are increased. It causes a significant increase in platelets, fibrinogen, factor V and VIII and fibrinolytic inhibitors (Philips et al, 1974) this is in marked contrast to saline infusion when used for abortion which causes decrease of all these levels. The increase in clotting factor is due to mild inflammatory process produced by prostaglandins.
7. **Effect on central nervous system**: There is small risk of generalized convulsion in normal patients and greater risk in persons with previous history of seizure (Sheerman et al, 1972).

8. **Lactation**: Sheerman et al, (1972) has reported a clearly high incidence of lactation following mid-trimester abortion by Prostaglandin.

**Complications**

Complications of Prostaglandins are not many but few may be very serious if not attended to in time.

1. **Haemorrhage**: This is most common complication. Duenhoetter et al (1975) has reported fall in Hb in 13.1% cases with intra-amniotic administration. Laursen and Wilson (1975) have described the blood loss between 75-150 ml in patients induced by intramuscular route.

2. **Infection**: Duenhoelter et al, (1975) has described the incidence requiring antibiotic therapy as 14.8% following intra-amniotic route. Laursen and Wilson (1975) have reported fever in 20% following induction by intramuscular route.

   Karim and Wuiquist (1973) have reported that only 5% cases have fever following intramuscular route, and cause of pyrexia by premature rupture of membrane.

3. **Uterine and cervical rupture**: Rupture of cervix are rare and serious complications as they interfere in future child bearing. Cervical rupture leads to future premature deliveries, while uterine rupture necessitates hysterectomy.

   Following intramuscular injection of PGF₂ alpha, Hernique et al, (1977) has reported cervical laceration in 2 out
of 63 patients. The cause was cervical dystocia. Hernique has also described ballooning of cervix in 2 patients without cervical dilatation. The cause of these tear is not very well understood. The tear had been mainly transverse and in posterior cervical lip. The cause could be either active cervical contraction or a very rapid onset of strong uterine contraction due to patient's cervix not getting time to dilate. This complication is mainly seen in young primigravid patients. To avoid this complication cervix should be dilated prior to myometrial contraction.

4. **Failure to abort**: Failure to abort is due to lack of sensitivity of uterus to Prostaglandins. Lauersen (1976) reported that when patient fails to abort she should be checked for uterine malformation and fibromyoma.

Prostaglandins are involved in every stage of human reproduction. Ever since von Euller gave the name 'Prostaglandin' to a substance found in the extracts and secretions from the human prostate and seminal vesicles there have been nearly yearly developments in the search of newer Prostaglandins with better efficacy and tolerance.

In 1968 Karim introduced Prostaglandin infusion (PGF₂) for induction of labour. In 1986 PGE₂ cervical gel (Dinoprostone) was introduced. The development of mifepristone began in 1980. In 1988 France was the first country, which use mifepristone in combination with Prostaglandin analogues.

In this series of researches Misoprostol was introduced by El-Refaey et al in 1995. Zeiman et al compared the absorption kinetics of misoprostol after oral and vaginal administration. In 1999 Lehavi et al first reported its intravaginal use.
The new synthetic analogue of PGE₁ (Alprostadil) is misoprostol. Naturally occurring PGE₁ is not orally sustainable as it is unstable in acid media, and also not suitable for parenteral use because of its rapid degradation in the blood. Synthetic PGE₁ analogue has been produced by bringing about an alteration in the chemical structure of this naturally occurring compound, thereby making it orally stable and clinically useful. The chemical formula of misoprostol is C₂₂H₃₈O₅ or (±) methyl (13E)-11, 16 dihydroxy-16methyl-9-oxo-prost-13-enolate by relocating the 15-hydroxy group to the adjacent 16 position and addition of a methyl group to carbon 16, misoprostol has developed from PGE₁.

![Chemical structure of misoprostol](image)

**Chemical structure of misoprostol**

Addition of a methyl group to the carbon-16 position, C-16 hydroxy group is less susceptible to the action of 15-dehydrogenase enzyme that inactivates natural PGE₁ (Collins PW) the carbon-15 position of the hydroxyl group has been shifted to the carbon-16 and this reduces the side effects, misoprostol contains approximately equal amounts of the two diasteromers presented below with their
enantiomers indicated by (±). Misoprostol is water soluble, viscous liquid.

**Pharmacodynamics and pharmacokinetics**

Misoprostol is manufactured as an oral preparation in 100μg and 200μg tablets. These tablets can be used orally, vaginally and rectally. After oral administration, misoprostol is rapidly absorbed and converted to it’s pharmacologically active metabolite, misoprostol acid, and is further metabolized by fatty acid oxidizing system present in numerous tissues of the body. The serum protein binding of misoprostol acid is less than 90% and is concentration independent in the therapeutic range. The bioavailability of misoprostol is decreased by concomitant ingestion of food or antacids. Misoprostol is primarily metabolized in the liver, and less than 1% of its active metabolite is excreted in urine. Patients with hepatic disease should receive a decreased dose, whereas dose adjustment is unnecessary for patients with renal insufficiency and in those who require dialysis. Misoprostol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system. Most nonsteroidal anti-inflammatory drugs do not produce any change in their kinetics when used with misoprostol, except clinically non-significant 20% decrease of aspirin activities. Similarly no drug interaction has been noted with antipyrine, propranolol and diazepam.

Absorption kinetics as studied by Zieman et al, (1997) proved that vaginal application is superior to oral administration. Vaginal application has the advantage of reducing gastrointestinal side effects and exerts profound effects on reproductive tract, thereby this route has been used extensively in different clinical conditions related to obstetrics and gynecology.
After application in the posterior fornix, plasma concentration reaches peak by one to two hour and then slowly declines unlike oral absorption. Slower increase and lower peak plasma concentration of misoprostol is noted in vaginal application when compared to oral application but overall exposure to drug is increased following vaginal application.

Following oral administration peak level is reached between 12.5 and 60 minutes and falls steeply by 120 minutes. In contrast, plasma concentration of the drug in women receiving vaginal dose, rises gradually and reaches maximum levels between 60 – 120 minutes. Plasma concentration declines slowly to an average of 61% of the peak level at 240 minutes after vaginal application and the bioavailability of the drug is 3 times higher than that after oral administration probably due to its by-passing the gastrointestinal and hepatic metabolism.

In vivo studies have shown that after oral and vaginal administration of the drug, intrauterine pressure begins to increase by 8 minutes and reached maximum by 25 and 46 minutes respectively. Uterine contraction exerted by this drug also differs when applied by different routes. After oral administration uterine contraction peaks up by next one hour and then attains plateau whereas uterine contraction rises continuously for next four hours after vaginal application, maximum uterine contractility was significantly higher after vaginal administration.

**Posology**

Unless given in a high dose, this drug does not produce any deleterious adverse effects. Though toxic dose of this drug is yet to be
determined, however, cumulative dose up to 2200 μg has been tried in varying doses from as low as 25 mg to 800 mg either alone or in combination with agents to achieve clinical efficacy.

**Adverse effects**

Like other prostaglandins misoprostol also has common gastrointestinal adverse effects such as nausea, vomiting, diarrhea, abdominal pain, dyspepsia, flatulence and constipation (rarely). Other dose dependent side effects are pyrexia, chills, shivering and headache. Skin rashes and dizziness have been infrequently reported. Myocardial infarction and bronchosasm has not been reported yet with misoprostol which are not uncommon with prostagland F_2α and E_2. Very high doses like 600 μg taken orally (with trifluoperazine) to terminate pregnancy has been reported with abortion, hyperthermia, rhabdomyolysis, hypoxemia. Gynaecological disorders like spotting, cramps, hypermenorrhoea, dysmenorrhoea and post menopausal bleeding have been reported in clinical trials in a small number of patients. Insignificant side effects involving different systems has been reported in clinical trials.

**Safety profile**

Though the toxic dose in humans has not yet been determined, acute toxic effects has been reported in animal studies in the form of diarrhoea, gastrointestinal lesions, focal cardiac necrosis, hepatic/renal tubular necrosis, testicular atrophy, respiratory difficulties and depression of central nervous system. Over dose has been clinically manifested by sedation, tremor, convulsion, dyspnoea abdominal pain, fever, dirreoea, palpitation, hypotension or bradycardia and should be treated with supportive therapy. It is not yet known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a
fatty acid, it is unlikely that dialysis would be appropriate treatment of overdose.

Misoprostol does not produce any significant effects on serum levels of prolactin, gonadotropins, thyroid stimulating hormone, growth hormone, thyroxine (somatostatin, gastrin, vasoactive intestinal polypeptide and motilin), (creatinine or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function or the cardiovascular systems are not modified by recommended doses.

**Teratogenicity**

Moebius’ syndrome (congenital facial paralysis) and limb defects have been reported occasionally in infants of women who ingested misoprosal in 1st trimester in an unsuccessful attempt to induce abortion. Among women who have delivered children affected with moebius’ syndrome, the likelihood of exposure to misoprostol in 1st trimester is very high. The absolute risk of this syndrome among all women exposed to this drug in the 1st trimester is possibly low. Localized ischemia in the placental bed and vascular disruption in the embryo are postulated as the operational mechanism for causing the congenital anomalies.

In a recent case control study, malformations like transverse limb defects ring-shaped constriction of the extremities, arthroryposis, hydrocephalus, holoprosencephaly and extrophy of bladder, but not moebius’ syndrome has been reported in infants.

**Mechanism of action**

Misoprostol is a synthetic PGE\textsubscript{1} analogue. It has actions mainly on gastrointestinal tract and uterus. Like endogenous PGE\textsubscript{1},
misoprostol exerts a protective effect on the gastrointestinal mucosa by increasing mucus and bicarbonate ion secretion and by increasing mucosal blood flow. In addition, misoprostol inhibits acid secretion. Misoprostol acts locally on the parietal cells to decrease acid secretion. It also exhibits local mucosal protection by supplying an exogenous source of prostaglandins. The principal active metabolite (misoprostol acid) is rapidly metabolized and absorbed following oral administration. Thus, it provides protection against the erosive effects of NSAIDS.

In addition, misoprostol is also myometrial stimulant, which binds to both E2 and E3 prostanoid receptors. It also has cervical ripening effects. Its active plasma metabolite is misoprostol acid. It is rapidly absorbed after oral, vaginal and rectal administration. 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.

**Comparative effectiveness of vaginal and oral administration of misoprostol**

*(EL Refaey et al. 1995)*

- More side effects with oral use
- At similar doses more effective by vaginal route
  - 95% (vaginal) success rate Vs 87% (oral) in first trimester
  - Failure 1% (vaginal) Vs 7% (oral)
- abortion within 4 hours : 93% (vaginal) Vs 78% (oral).

It is assumed that rectal administration results in a similar profile, vaginal dosing therefore can take place with longer intervals
than oral dosing for similar desired uterine effect, and accumulation above 'safe' levels with undesirable side effects can take place. With oral and vaginal dosing of up to 400μg every 3 hours, no accumulation has been noted. Potential hypertonus as a result of drug accumulation could lead to:

- Uterine rupture in the second or third trimester
- Fetal distress in the third trimester
- High rates of nausea and diarrhoea in all trimesters.

For obstetrical use, the vaginal application has been studied the most. Misoprostol in the first and second trimesters is an effective pregnancy termination agent either as a single agent or as an adjunct.

In our study misoprostol has been used vaginally in dose of 400μg 4 hourly as mid-trimester abortifacient along with oxytocin as and when needed. Misoprostol in this dose has been compared to traditional use of dinoprostone in 0.5 mg 12 hourly dosage.

Different studies have been done using misoprostol either alone or with adjuncts using different protocols for mid-trimester abortion. The abortifacient dose of misoprostol is in between 50-800μg and the exact dose schedule is yet to be decided.

**Bugalho et al.** In 1993 used 200μg to 800μg misoprostol intravaginally every 24 hourly with success rate of 91% within 48 hours and mean induction abortion interval of 14.3 hours.

**Jain and Mishell** in 1994 compared 200μg 12 hourly intravaginal misoprostol with 20μg vaginal gemeprost 3 hourly and found 89% success rate with misoprostol compared to 81% success.
rate with gemeprost and mean induction abortion intervals were 12 hrs and 10.6 hrs respectively.

Jain and Mishell in 1996 compared 200µg 12 hourly intravaginal misoprostol with combination of misoprostol + laminaria tent and found 84.80% success rate with misoprostol alone compared to 91% success rate when used with laminaria tent. Mean induction abortion intervals were 15.7 hrs and 17.4 hrs respectively.

Batioglu et al. in 1997 gave 200µg oral misoprostol 1 hourly (maximum 6 doses) and repeated on 2nd day if no abortion occurred. The success rate was 92.9% within 48 hrs and mean induction abortion interval was 9 hrs.

Srisomboon in 1997 used 200µg cervicovaginal misoprostol 12 hourly and success rate was 54% within 12 hours and 92% within 48 hours with mean induction abortion interval of 27.5 hours.

Carbonell et al in 1998 used 800µg vaginal misoprostol 24 hourly for 3 doses with success rate of 80% and mean induction abortion interval of 9.1 hours.

Dickinson et al in 1998 compared 200µg 6 hourly vaginal misoprostol (maximum 4 doses) with 1 mg vaginal geneprost 3 hourly (maximum 5 doses) with success rate of 74.9% within 24 hours for misoprostol and 75.1% for gemeprost. Mean induction abortion intervals were 16.9% hours and 13.7% hours respectively.

Herabutya et al in 1998 used 200µg and 600µg vaginal misoprostol 12 hourly for 48 hours and found success rate of 70.60%,
82.0% and 96.0% respectively. Mean induction abortion interval were 45 hours, 33.4 hours and 22.3 hours respectively.

Wong KS et al in 1998 compared 400μg 3 hourly vaginal misoprostol with 1 mg 3 hourly vaginal gemeprost and found success rates of 80% and 58.6% within 24 hours respectively. Mean induction abortion interval was 14.1 hours and 19.5 hours respectively.

Ghorab et al in 1998 compared extra-amniotic PGF2 with intracervical misoprostol and found abortion was complete in 65% and 85% cases respectively.

Premila W. Ashok et al in 1999 used miferpristone 200 mg orally in women for mid-trimester abortion, followed 36-48 hours by intra-vaginal misoprostol 800μg. Further, oral misoprostol 400μg was administered at 3 hourly interval (maximum 4 dose) 97% women aborted successfully either within 5 doses of misoprostol or within 15 hours of first dose of misoprostol.

Jain et al in 1999 compared 200μg vaginal misoprostol 6 with 200μg vaginal misoprostol 12 hourly and found success rate of 87.2% and 89.2% in 48 hours respectively. Mean induction abortion intervals was 13.8 hours and 14 hours respectively.

Herabutya et al in 2000 used 600μg vaginal misoprostol 12 hourly until abortion and found 93% success rate within 72 hours and mean induction abortion interval was 24.1 hours.

Wong KS et al in 2000 compared 400μg vaginal misoprostol 3 hourly with 400μg 6 hourly and found success rates of 90.5% and
75.7% within 48 hours. Mean induction abortion interval was 15.2 hours 19 hours respectively.

**Herabutya et al** in 2001 compared 600µg vaginal misoprostol 12 hourly with 800µg vaginal misoprostol 12 hourly and found success rate of 92.5% and 92.15% within 48 hours. Mean induction abortion interval was 15.2 hours and 15.3 hours respectively.

**Pongasta et al** in 2001 used 400µg vaginal misoprostol gel (formed by crushing the tablet and mixing with K-Y jelly) 12 hourly and found mean induction abortion intervals of 35.58 hours.

**Hidar S et al** in 2001 compared 200µg misoprostol vaginal 12 hourly with 200µg misoprostol vaginal combined with oxytocin infusion. The abortion was successfully in 90% and 95% at 48 hours.

**Gonzalez et al** in 2001 compared 200µg vaginal misoprostol 6 hourly in admitted patients with same dosage self administrated by patients at home and found mean induction abortion interval of 12 hours and 14 hours respectively.

**Dickinson et al** in 2002 compared 200µg 6 hourly with 400µg 6 hourly and also with 200µg vaginal misoprostol (following a loading dose of 600µg) and the success rates were 59%, 76% and 80% respectively within 24 hours with mean induction absorption interval of 18.2 hours, 15.1 hours and 13.2 hours respectively.