1 INTRODUCTION

1.1 Preface

At present, induction of labour in viable pregnancies is mainly performed with prostaglandin (PG) E_2 derivates such as Prepidil®, Prandin® and Minprostin E_2®.

Recently a new agent, misoprostol, a prostaglandin E_1 analogue, has been discussed as an ideal alternative for induction of labour at term in viable pregnancies apart from other options of indication, such as cervical ripening before hysteroscopy, induction of abortion and therapy of postpartum haemorrhage.

Misoprostol (Cytotec®) was manufactured by Searle Pharmaceuticals for prophylaxis and therapy of gastro duodenal ulcer in the early 70s. It has been available in 100-µg and 200-µg tablets on the international market since 1986. In Germany, it is registered for the purpose mentioned in 200-µg tablets.
The instruction leaflet indicates the contraindication in pregnancy.

Misoprostol's advantages over dinoprostone preparations are the high efficacy, the stability against light and changes in temperature, the easy mode of application and the low costs [1,2]. The price of one 200 µg tablet misoprostol is 0.30 € as compared with 26 € for 0.5 mg Prepidil®-Gel for intracervical application, to 34.50 € for one Gemeprost vaginal tablet (Cergem®) or 72 € for one Propess® vaginal insert [2].

Up to now, Searle Pharmaceuticals, now incorporated into Pfizer, has been warning against the use of misoprostol in pregnancy although the American College of Obstetricians and Gynaecologists (ACOG) confirmed efficacy and safety in cervical ripening, induction of labour and therapy of postpartum haemorrhage.

One of the main concerns described in former literature was the higher incidence of tachysystole after the application of misoprostol for induction of labour in viable pregnancies [3].

The aim of our studies was to evaluate the efficacy and safety firstly of misoprostol applied orally or vaginally in comparison with the standard treatment using intravaginal prostaglandin E_2 gel, dinoprostone, and secondly the combination of vaginal and oral misoprostol as compared with the oral application of misoprostol.
Both, efficacy and safety are likely to be dose related.
There are two possible methods of reducing the potency of the drug: the dose of the drug can be decreased, or the dosage interval can be prolonged. Most studies used doses of 25 µg or 50 µg misoprostol every 3 to 4 hours [4].

Two studies have been planned and carried out at Groote Schuur and Mowbray Maternity Hospital in Cape Town, South Africa.
In the main study with 480 patients, the goal was to reduce adverse events by a 6-hourly application of 50 µg misoprostol and compare the results to the standard prostaglandin E_2 gel.
The choice of the dosing interval was influenced by the pharmacokinetic findings of Zieman et al. It was described that after a dosage of 400 µg misoprostol vaginally the active metabolite fell to an average of only 61% of the peak level after 240 minutes [5]. To avoid accumulation and adverse events, the interval chosen between the applications was 6 hours.

In the course of the main study it was noted that compared with the oral application, repeated vaginal application of misoprostol was associated with an increased incidence of tachysystole and cesarean sections for fetal distress. At the same time, the oral administration of misoprostol was less effective than the vaginal route or dinoprostone when given every 6 hours. It was concluded that oral misoprostol should rather be given every 4 hours to enhance efficacy.

Hypothetically, an initial dose of vaginal misoprostol followed by subsequent oral doses could possibly maintain efficacy and reduce adverse events.
The vaginal oral regimen had already been suggested as being highly effective in mid-trimester termination of pregnancy [6].
The pilot study with a number of 40 nulliparous patients evaluated the vaginal oral regimen with an application interval of 4 hours for induction of labour at term.

1.2 Prostaglandins in the Reproductive World

The discovery of the contracting effect of seminal fluid on uterus is claimed by Kurzrok and Lieb, Columbia University, New York. In 1930, they observed the contractile effects of fresh human seminal fluid on strips of the human uterus [7]. The extraction of lipid-soluble material from seminal fluid and its stimulation of smooth muscle preparations were described independently by Goldblatt in England [8] and von Euler in Sweden somewhat later. Von Euler reported that this biological activity was due to an acidic lipid, which he named *prostaglandin,* assuming that the substance was exclusively produced in the prostate [9]. Only in 1963 did Eliasson find that the biological activity takes place in the seminal produced in the seminal vesicles [10].
In 1957, Sune Bergström succeeded in extracting crystalline prostaglandin from large batches of sheep seminal vesicles. In the early 1960s, he discovered the characteristics and synthesis of prostaglandins [11]. Shortly afterwards, the total synthesis of prostaglandins was achieved.
Anggard was responsible for the first biosynthesis of fatty acid precursors [12].

Prostaglandins were reported to be used for the first time in the reproductive world in 1968. Sultan Karim reported a successful induction of labour at term in women in Uganda with a $PGF_{2\alpha}$ intravenous solution. It was soon discovered that PGE_2 and $PGF_{2\alpha}$, unlike oxytocin, are effective agents for stimulating the uterus also in early pregnancy [13,14]. Shortly after these initial trials, more literature appeared about various ways of prostaglandin administration: intraamniotically, extraamniotically and intravaginally [15].
Since that time, different preparations of PGE_2, PGE_1 and $PGF_{2\alpha}$ have commonly been used for diagnostic and therapeutic hysteroscopy, first and second trimester termination of pregnancy, induction of labour and for treatment of postpartum haemorrhage.

Misoprostol, a prostaglandin E_1 analogue, has been sold internationally by Searle pharmaceuticals since 1986 for prophylaxis and therapy of gastroduodenal ulcer.
An uterotonic effect of misoprostol was first described in 1988 in Brazil after purchase "over the counter" followed by self-medication for illegal abortion. Several trials followed using misoprostol for the induction of abortion in first and second trimester pregnancies.
Since 1993 a variety of studies comparing misoprostol to the usual preparations for induction of labour at term have been published.

1.3 Prostaglandins' Biochemistry

1.3.1 Structure and Nomenclature

Prostaglandin is a generic term for a closely related family of oxygenated, poly-unsaturated C20 fatty acids containing a cyclopentane ring (Figure 1-1). They derive from the hypothetical prostanoic acid.

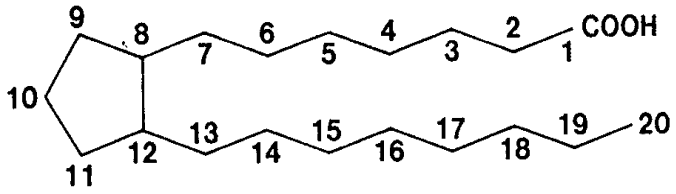

Figure 1-1: Hypothetical prostanoic acid skeleton [16].

Nine groups (A, B, C, D, E, F, G, H and I) of prostaglandins have been differentiated to date. They have been given capital letters in alphabetical order. Each capital letter refers to a specific chemical structure in the cyclopentane ring [16]. The amount of double bonds in the two side chains is indicated by the number of subscript numerals, for example PGG2 or PGG3. The Greek letters alpha and beta describe the steric configuration of the hydroxyl substituent on the C-9 position relative to the average plane [17].

1.3.2 Biosynthesis and Activity

The natural prostaglandins with the greatest biological activity are those with two double bonds deriving from arachidonic acid [18].

Arachidonic acid can be obtained directly by diet or synthesised from its precursor linoleic acid, which is an essential fatty acid that cannot be synthesised *de novo* in human tissues. Its formation will depend on the composition of the diet and its manipulation [19].

Dihomo-γ-linolenic acid, which has one less double bond than arachidonic acid, gives rise to the prostaglandins of the subscript-1 series [20].

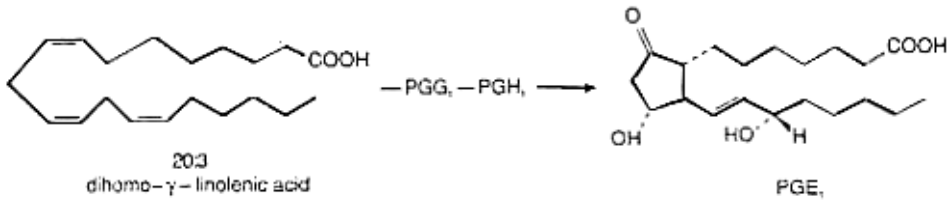

Figure 1-2: PGE_1 synthesis [21].

Most C20-fatty acids among the phospholipids and esterified cholesterol are built from esterified arachidonic acid. The initial step for the prostaglandin synthesis of the subscript-2 series is the release of arachidonic acid by a variety of hydrolases, especially the phospholipase A2 [20].
All the 20-carbon derivate products descending from arachidonic acid are called "eicosanoids", while those containing a structural ring are named "prostanoids".
After the release of the arachidonic acid, the synthetic path leads in two different directions: the lipoxygenase pathway or the cyclooxygenase -prostaglandin endoperoxide H synthetase-pathway.

The first of the two leads to hydroxyeicosatetraenoic acid and leucotriens which are involved in the defence reactions of white cells and participate in hypersensitivity and inflammatory responses such as asthma and airway obstructions.

The enzyme cyclooxygenase (COX) is the key intermediate for the 2-doublebound-prostaglandins and catalyses the transformation of arachidonic acid into PGG_2 and the subsequent reduction to PGH_2 [22]. The activity of specific synthases and isomerases is responsible for the following formation of prostaglandins, including thromboxane (TXA2) [23] and prostacyclin [24] (Figure 1-3).

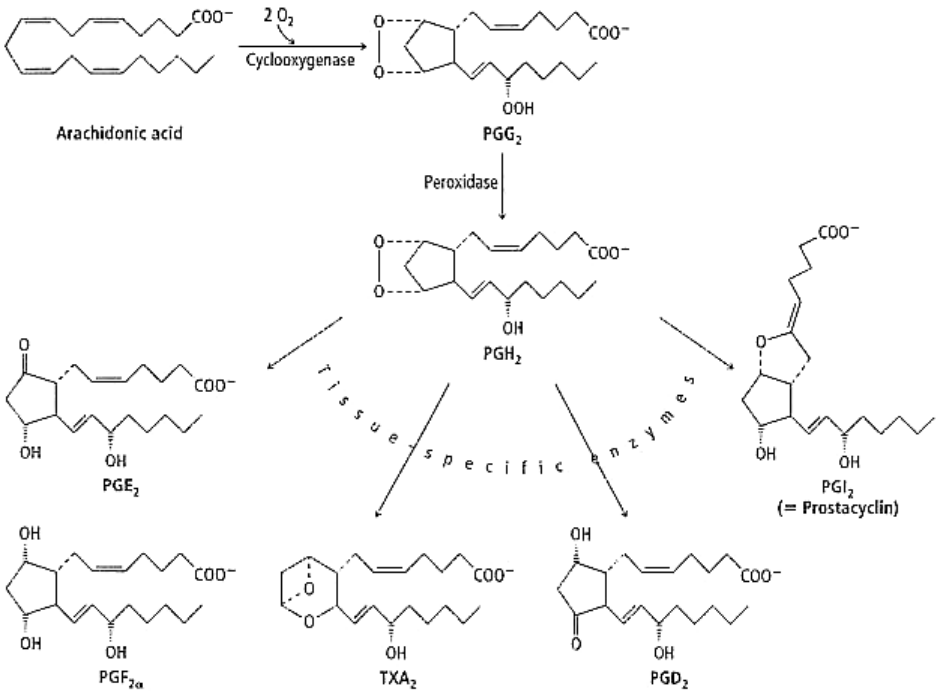

Figure 1-3: Synthesis of Prostaglandins [25].

Christ and van Dorp found extremely high activity of prostaglandin synthetase in vesicular glands (75% of the conversion of the substrate) and other tissues like that of lung, kidney and the gastrointestinal tract of animals [26].
The resulting products of the transformation depend on the local tissue.

The prostaglandins of original and continuing relevance to reproduction are PGE_1, PGE_2 and $PGF_{2\alpha}$. These groups are potent stimulants for the uterus at any stage of pregnancy.

1.3.3 Metabolism

In man, most of the primary prostaglandins are metabolised during the first passage in the body primarily in the lungs, kidneys and liver [27].
The half-life of naturally occurring prostaglandins is only seconds to some minutes long. The estimated plasma half-life of intravenously administered PGE_2 is less than one minute, whereas that of the major metabolite is approximately 8 minutes. Similar data were obtained for $PGF_{2\alpha}$ [28,29].
For medical purposes, they have therefore been replaced by prostaglandin analogues.

The metabolisation of prostaglandins occurs in consecutive steps:

- The initial most rapid step is the oxidation of the 15-hydroxy group to a keto group followed by the reduction of the 13,14 double bond to a 13-14-dihydro-15-keto compound. This metabolite no longer shows biological activity.
- The next process is β-oxidation of the carboxyl side-chain.
- Another point of attack is the ω-chain terminus.
- The wide variety of products are mostly excreted in the urine [30,31].

1.3.4 Prostaglandin Inhibition

The inhibition of the biosynthetic cascade of products is the key to various treatments in the medical field.
Corticosteroids block the activity of the phospholipase [32] by synthesis of proteins called lipocortins or annexins [33].
The inhibition of the cyclooxygenase enzyme is the mechanism by which acetylsalicylic acid (aspirin) and nearly all non-steroidal anti-inflammatory agents prevent the formation of classical prostaglandins [34].

Administration of indomethacin during labour results in a significant reduction in the synthesis of PGE_2 and $PGF_{2\alpha}$. It has widely been used to suppress unwanted uterine activity [35,36].

1.4 Physiology and Use of Prostaglandins in Gynaecology and Obstetrics

1.4.1 Prostaglandins and Luteal Regression

Prostaglandin $F_{2\alpha}$ production by the primate and human corpus luteum is well established, just like the changes in relative concentrations of PGE_2 / $PGF_{2\alpha}$ and their binding sites in early, mid- and late corpora luteal phases. The number of binding sites has been shown to vary with the age of the corpus luteum during the human menstrual cycle.

The early luteal phase is characterised by elevated PGE_2 concentrations, corresponding to peak progesterone levels, while the late secretory phase is associated with lower progesterone levels and markedly higher $PGF_{2\alpha}$ [37,38].

In most mammals, $PGF_{2\alpha}$ originates in the endometrium. Recent studies have proposed that in humans, endometrial / extraluteal $PGF_{2\alpha}$ initiates luteolysis whereas luteal $PGF_{2\alpha}$ may contribute to structural luteolysis [39]. The high concentration of the agent is responsible for terminating the lifespan of the corpus luteum if fertilization fails to take place [40,41].

1.4.2 Fetal Circulation

In the fetal and maternal cardiovascular system, prostaglandins are responsible for keeping the ductus arteriosus and other arteries in a relaxed or dilated state. With increasing gestational age, the ductus becomes increasingly responsive to elevated oxygen levels with constricting consequences. PGE_2 is the most potent vasodilator of the ductus and is more responsive to oxygen than PGI_2 and other prostaglandins. PGI_2 is the major factor for vasodilatation in the pulmonary bed [42]. With the onset of pulmonary ventilation at birth TXA_2, increasingly produced in the lungs towards term, now serves as the vasoconstrictor stimulus together with oxygen [43].

Infants with persistent ductus patency are treated with prostaglandin inhibitors such as indomethacin [44].

Prostaglandins are indicated as medicament in neonates with duct dependant congenital heart anomalies. Prostaglandin E_1 can effectively maintain the patency of the ductus arteriosus beyond the first week of life [45,46].

1.4.3 Cervical Changes and Myometrial Contractility

In normal pregnancy, the uterine myometrium does not contract effectively until term. Existing contractions usually do not cause changes in the cervix.

It is plausible that there exist some mechanisms to block the uterine contraction during pregnancy and others to cause myometrial contractions, cervical ripening and initiation of parturition at term.

The uterotonic effect of oxytocin is diverse.
The activity of oxytocin is mediated by a specific receptor. The receptor concentration is hardly present in the non-pregnant state. In pregnancy the receptor concentration in the myometrial cells at a gestational age of 13 to 17 weeks is low and increases in density until term [47].
Oestrogen and progesterone are major regulators of uterine oxytocin and its receptors. Oestrogen seems to upregulate both, whereas progesterone appears to have a positive effect on oxytocin but a negative effect on oxytocin receptors [48].
The plasma concentrations of PGE and PGF rise during oxytocin administration [49], which stimulates the production of those prostaglandins from human deciduas [50].
Recently, it was reported that oxytocin also induces the expression of cyclo-oxygenase II releasing prostaglandins into the myometrial cells [51].

The myometrial smooth muscle cells communicate with one another through gap junctions, low resistant pathways, which synchronise the contractile function by conducting the electrophysiological stimuli during labour. These gap junctions increase in number and density in the final weeks of pregnancy, when irregular contractions increase and cervical maturation occurs [52].
Gap junction formation is related to the oestrogen / progesterone ratio - estrogens is stimulatory and progesterone is inhibitory - and to the presence of PGE_2 and $PGF_{2\alpha}$ [53].
PGE_2 and $PGF_{2\alpha}$ stimulate myometrial contractility most likely by modulation of calcium fluxes.
The final contraction of uterine muscle results from increased free calcium concentration in the myofibril as a result of prostaglandin action [54-57].

Prostaglandins E_2 and $F_{2\alpha}$ are synthesised at the site of action by the amnion, decidua and myometrium of the parturient women [58].
Reece et al. described an increase in the prostaglandins E_2 and $F_{2\alpha}$ in the foeto-placental unit towards term [59].

An accepted concept of parturition suggests that the hypothalamic-pituitary-adrenal-placental axis is responsible for the alteration of the placental steroidgenesis towards the end of gestation.

The progesterone output declines, the estradiol production increases towards term. The estradiol / progesterone ratio increases [60]. This might lead to stimulation of oxytocin, oxytocin receptors, gap junction and PG synthesis. During the last weeks of gestation, a parallel increase in placental corticotropin releasing hormone and fetal cortisol levels has been observed [61].
Whittle et al. suggest that towards the end of gestation in sheep there is an increase in the placental throphoblast expression of prostaglandin H synthase-II expression and PGE_2 production under the regulation of fetal cortisol produced from the maturation of the fetal hypothalamic-pituitary-adrenal axis. Placental PGE_2 promotes placental oestrogen production and acts to sustain fetal hypothalamic-pituitary-adrenal axis activation. Oestrogen up-regulates the expression of maternal endometrial prostaglandin H synthase-II and PGF_2 output. Consequently, myometrial activity is stimulated [62].

Inflammatory agents play an important role in the initiation of labour as they stimulate the synthesis of prostaglandins [63,64] and at the same time decrease the metabolism [65].
Preterm deliveries associated with infection are characterised by an increased level of cytokines - such as interleukin (IL)-1β, IL-6, IL-8 and tumour necrosis factor-α - in the fetal membranes [66], amniotic fluid [67-69], lower genital tract [70], and the uterus [71].
Also in normal deliveries at term without infection, there are increased levels of IL-8 in the myometrium [72], IL-1β and IL-8 in the amnion and the chorio-decidua [73].

For the mechanism of cervical ripening the most important sources of prostaglandins seem to be the decidua for $PGF_{2\alpha}$ production and the amniotic membranes for PGE_2 production [74].
The smooth muscle of the cervix responds with relaxation, the fundal myometrium with contraction [75].
Local application of dinoprostone evokes different mechanisms that lead to cervical ripening. Prostaglandins lead to enzymatic changes that induce collagen breakdown, rearrangement of collagen fibres and an increase in tissue water content. It also influences the activity of collagenase, elastase as well as the total levels of glycosaminoglycan, dermatan sulphate and hyaluronic acid [76,77]. Rising concentrations of hyaluronan are considered to be inducers of IL-1 and tumornecrosis factor-α synthesis. The resulting increase in IL-6 stimulates the prostaglandin and leukotriene production. This leads to a dilatation of cervical vessels, the chemotaxis and degranulation of leucocytes and macrophages followed by an enzymatic collagen degradation [78].

The activity of prostaglandins suggests that the myometrium expresses specific prostaglandin receptor isoforms to regulate contractility [79,80]. The receptors are present in pregnant and non pregnant uteri [81].

Eight receptor subtypes have been described: contractile isoforms EP1, EP3, FP, thromboxane and the relaxatory isoforms EP2, EP4, IP, DP [82,83].

Prostaglandins affecting their specific receptor can induce opposite reactions depending on the type of receptor, the concentration and affinity of the prostaglandin on the receptor and the receptor density expressed at that stage of gestation.

Prostaglandin E_2 binds to four distinct receptors which are linked to the contractility (EP1, EP3) in smooth muscle by inhibiting the adenylatecyclase system and raising intracellular calcium or quiescence (EP2, EP4), by stimulating the adenylatecyclase system and increasing cAMP [82]. The distribution of receptors may also be important with regard to uterine contractility in pregnancy. Contraction-promoting receptors are more frequent in the fundus, whereas relaxation-promoting receptors are found in the lower uterine segment [84].

Prostaglandin receptor affinities for prostaglandins in human myometrium vary in nonpregnant and pregnant uteri. The affinity of the ligands PGE_1 and PGE_2 to the $PGF_{2\alpha}$ receptor (FP) is higher than that of $PGF_{2\alpha}$ itself [85].

The receptor expression changes throughout pregnancy, thus, influencing the mode of response towards prostaglandins depending on gestational age.

It has been shown that the quiescent EP2 receptor expression is high before term and declines significantly with advancing gestational age, pre-term or at term. The FP receptor expression is low before term, decreases with gestational age and increases dramatically at term, also in pre-term women in labour.

Theoretically pre-term labour could be explained by the rising FP receptor concentration up to where the still highly expressed quiescent EP2 receptors can no longer counteract the up-regulation, which may lead to a change from a quiescent to a contractile uterus and parturition. This balance shift of these two receptor isoforms could lead to uterine contractions and the onset of labour [86].

Matsumoto et al. reported that the expression of EP3 and FP genes in pregnant uteri is reduced to 50% compared with that in non pregnant myometrium. This leads to the conclusion that the down-regulation of these contractile receptors influences the maintenance of quiescence in normal pregnancy [87].

1.5 Prostaglandins for Cervical Ripening and Induction of Labour

1.5.1 Dinoprostone

Until today, the preferred prostaglandin agent used for cervical ripening and induction of labour at term has been PGE_2.

A few years after the introduction of prostaglandins for the induction of labour, low doses were found to cause a marked softening of the uterine cervix [88]. It has been reported to be an effective and safe method for cervical softening and induction of labour when induction is indicated [89].

Common side-effects are nausea, vomiting, diarrhoea, rise of temperature, lowered blood pressure, uterine hyperstimulation and fetal distress.
In patients with compromised cardiovascular, hepatic or renal function and those with asthma and glaucoma, it should be used with caution as PGE_2 and $PGF_{2\alpha}$ are known to influence those systems.

The half-life of PGE_2 in the circulatory system after injection is less than 30 seconds while that of the inactive metabolites is about 10 minutes.
PGE_2 is metabolised by oxidation at C15, reduction of 15-keto-PGE_2 and then oxidation of the β- and ω-side chains to 7α-hydroxy-5,11-diketo-prostane,16-dioic acid, which is excreted in urine [30].

Oral administration of PGE_2 is not recommended for clinical use as it shows a short half-life of some seconds and is associated with a higher rate of maternal side effects than the vaginal application [90,91].

Absorption of PGE_2 after vaginal administration is dependent upon the administration medium. Frequently peak levels of 11-deoxy-13,14-dihydro-15 keto-11,16 w-cycle PGE_2 (bicyclo PGEM), a stable metabolite, are found within 30-120 minutes of treatment and are maintained for the subsequent 3-6 hours [92].

Keirse et al. performed a worldwide meta-analysis in 1993 evaluating the effectiveness and safety of prostaglandins for the ripening of the cervix.

It was found that especially PGE_2 was a successful cervical ripener, which increased the pelvic score, showed significantly less failed inductions of labour, a higher number of patients delivering within 12 to 24 hours and a decreased incidence of prolonged labour compared with placebo or no treatment. The overall cesarean section rate could be decreased significantly and an increase in spontaneous deliveries was noted.

The study also showed that PGE_2 can be used in much lower doses than $PGF_{2\alpha}$, which was the first compound to be introduced for obstetrical purposes. Lower doses are less likely to cause side effects such as uterine hypertonia and hyperstimulation [93].

Keirse et al. concluded that $PGF_{2\alpha}$ should no longer be used for the induction of labour [94].

Extraamniotic PGE_2 gel and the 20 mg intravaginal suppository was abandoned because of uterine hyperstimulation [94].

Trials comparing the 0.5 mg intracervical PGE_2 gel with 2.5 mg vaginal gel or the vaginal controlled release reported the intravaginal route to be superior [95,96].

Nowadays, local application of PGE_2 preparations for cervical ripening and induction of labour are widely used. Different forms are available:

- Dinoprostone vaginal gel of 1 mg or 2 mg administered into the posterior fornix repeated 6-hourly (e.g. Prandin E2®, Pharmacia & Upjohn)
- 0.5 mg endocervical preparation of dinoprostone gel (e.g. Prepidil®, Pharmacia & Upjohn), Prepidil® can be given with a dosing interval of 6 hours.
- Dinoprostone vaginal insert (e.g. Propess®, Ferring Arzneimttel GmbH) contains 10 mg Cervidil. It releases dinoprostone by a controlled formulation at a rate of approximately 0.3-0.4 mg/hour for 12 or 24 hours.
- 0.5 mg dinoprostone tablet taken orally every hour until adequate uterine activity is attained (e.g. Prostin E2®, Pharmacia & Upjohn).
- 3 mg tablets or vaginal gel of 1 mg or 2 mg dinoprostone (e.g. Minprostin E2®, Pharmacia & Upjohn)

All these widely used preparations have two disadvantages: They are expensive and difficult to store. The compounds require continuous refrigeration until shortly before administration.

The price of a 0.5 mg dose of endocervical gel (Prepedil®) is 26 € and for one 10 mg vaginal insert (Propess®) 72 € [2].

1.5.2 Synthetic Prostaglandin E_1 Analogues

Synthetic prostaglandin E_1 analogues were developed for three reasons: the possibility of oral administration, a more durable effect and high biological activity in comparison to the naturally occurring agents.

In the beginning, the lack of oral activity of prostaglandins was attributed to the very rapid oxidation of the C15 hydroxy group to the corresponding ketone. The first prostaglandin that showed oral activity was synthesised in 1973 by blocking the oxidation of the hydroxy group at C15 adding either a methyl group at C15 or two methyl groups at C16. This blockage is a steric inhibition [97].

The final step was achieved by adding a methyl-group to C16 of the synthetic 16-hydroxy prostaglandin to reduce the oxidation of the C16 hydroxy-group which is also a substrate for the 15-dehydrogenase.

In 1973, Misoprostol, an analogue with gastric antisecretory potency equivalent to PGE_1, was developed by Searle Pharmaceuticals for the treatment of peptic ulcer disease [98].

These analogues became available for clinical use in gynaecology and obstetrics:

- Carboprost ((15S)-15-methyl-prostaglandin F2α tromethamine) by Upjohn Co, Kalamazoo, MI is used intramuscularly for mid-trimester termination of pregnancies. Compared with intravaginal PGE2 it is less effective 99.
- Gemeprost (16, 16-dimethyl trans delta PGE1 methyl ester) by Farillon Pharmaceuticals, UK is available as a 1 mg vaginal pessary and administered 3-hourly for first- and second-trimester termination 100,101. Pre-treatment with mifepristone shortens the duration of labour immensely 102. The disadvantage is the high cost of gemeprost, its need for special storage and the vaginal application.
- Meteneprost (9-deoxy-16, 16-dimethyl-9-methylene PGE2) by Upjohn Pharmaceuticals, UK
- Sulprostone (16 phenoxy-17, 18, 19, 20-tetranor-PGE2 methyl sulphenylamide) by Schering Pharmaceuticals has been voluntarily withdrawn by the company. Before that, it was the preferred agent used for termination of pregnancies as it was cheap and allowed flexibility in dose selection.
- Sulprostone infusion is still used in the treatment of postpartum haemorrhage.
- Misoprostol (DL-methyl-11α-16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate) by Pfizer

1.5.3 Mifepristone

Mifepristone, also known as RU 486, was developed by Roussel-Uclaf in 1988. It derives from the progestin norethindrone and acts as an antiprogestin agent. It is known to cause cervical changes and an increase in uterine activity. It has been the object of studies for menstrual regulation, abortion, induction of labour, treatment of breast cancer, ovarian cancer, meningiome and adrenal disorders. Clinically, mifepristone is effectively used in first trimester termination of pregnancies and cervical priming in second trimester terminations [103,104]. Nowadays it has preferably been used in combination with misoprostol [105].

1.6 Misoprostol

1.6.1 History of Misoprostol

Misoprostol was manufactured by Searle Pharmaceuticals in the early 1970s. This prostaglandin analogue was developed for prophylaxis and treatment of gastric and duodenal ulcers caused by non-steroidal anti-inflammatory drugs. It has proved an effective and safe substance for the treatment of gastroduodenal ulcers [106]. Misoprostol (Cytotec®; Searle, Chicago, IL) was released in 1986 on the international market for routine clinical use as an oral preparation of 100 µg or 200 µg tablets with a maximum recommended dose of 800 µg per day. The use during pregnancy was contraindicated due to an uterotonic effect with the risk of miscarriage [107].

Because of the rising quantities of misoprostol purchased over the counter and misuse as an illegal abortificant, a retrospective study was carried out in Brazil in 1988. It showed that 12% of the women admitted for abortion complications with requirement of uterine evacuation had used misoprostol to induce abortion. In 1991, 75% of such cases noted in Forteleza were related to misoprostol [108-110]. In one hospital in Rio de Janeiro women had reported having taken doses between 200 and 16,800 µg both orally and vaginally [111].

The attention of scientists was caught when it was discovered that misoprostol was used as a self administered abortificant provoking uterine contractions.

Early studies with women in the first trimester who used the drug to terminate pregnancy have demonstrated an uterotonic effect after oral administration of misoprostol, though misoprostol was reported to be a weak abortificant at doses of 2 x 200 µg or 2 x 400 µg [112].

Misoprostol seemed to be a cost-effective alternative with less complicated storage requirements than dinoprostone. It is easy to administer as it can be taken orally, buccally, vaginally and rectally.

1.6.2 Pharmacology

Misoprostol has a molecular weight of 382.54. It exists as an approximate 1:1 mixture of two diastereomers [113]. The compound produced by Searle Pharmaceuticals was approximately 35 times more active than the 16 hydroxy compound. Its selectivity was improved (cf. Figure 1-4) [114-116].

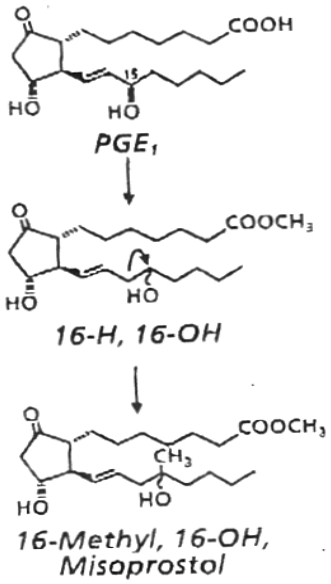

Figure 1-4: Discovery of misoprostol [117].

Problems of chemical instability were gradually reduced by dispersion of misoprostol in 1:100 hydroxypropyl methyl cellulose without influencing the pharmacology of the drug [118]. Conventional tablets of misoprostol have a shelf life of several years [117].

The administration of oral misoprostol with food slows down absorption relative to fasting, as shown in a reduction in maximum concentration (Cmax: 811 ± 317 pg/ml vs. 303 ± 176 pg/ml) and an increase in time to Cmax (14 ± 8 min vs. 64 ± 79 min) after 400 µg . It also results in a decreased bioavailability [119].

Misoprostol is metabolised by the fatty acid beta and omega oxidation system. After oral and vaginal administration it is rapidly absorbed and de-esterified to its biologically active metabolite, misoprostol acid. Further metabolic conversion occurs over time via beta-oxidation of the alpha side chain, omega-oxidation of the beta side chain and reduction to different prostaglandin analogues [120].
The efficacy of vaginal misoprostol application for cervical ripening and labour induction at term does not seem to be influenced by the vaginal pH [121].

Studies in humans and animals demonstrated a biphasic elimination of misoprostol acid with a terminal half-life of 20 to 40 minutes. Renal excretion of radio-labelled misoprostol over a seven-day period accounts for 73.2% ± 11.3% of the administered dose while 14.7% ± 7.7%

were excreted in the faeces. Less than 1% of the unchanged drug is detected in the plasma or urine [113].

Misoprostol-free acid exerts the effects via binding to specific receptors [122,123] and influencing second messenger systems through G-proteins. It is an agonist on EP1, EP3 receptors, and it activates EP2 and EP4 receptors. On EP4 receptors, it is a key differentiating agonist [124].
Misoprostol causes an increase in cAMP levels on EP3>EP2>EP1 receptors [125].

Zieman et al.'s study about absorption kinetics compares the oral to the vaginal administration of misoprostol using a dose of 400 µg. The plasma concentration after oral administration of misoprostol rises quickly, peaks after 34 ± 17 minutes and falls steeply after 120 minutes. The maximum plasma concentration was 277 ± 124 pg/ml. After vaginal misoprostol, the misoprostol acid concentration in the plasma rises gradually, reaches the maximum levels of 165 ± 86 pg/ml at 80 ± 27 minutes and declines slowly, to an average of 61% of the peak level at 240 minutes (Figure 1-5).

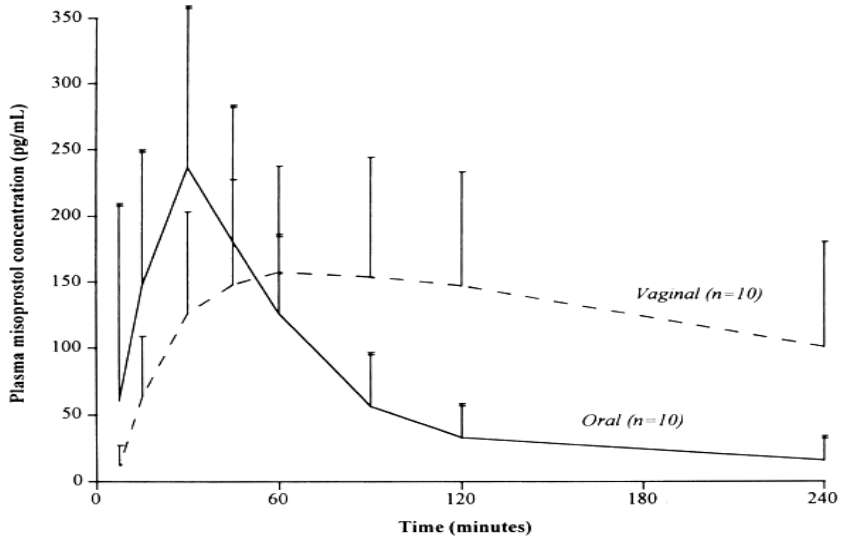

Figure 1-5: Mean plasma concentrations of misoprostol acid over time with oral misoprostol (solid line) and vaginal misoprostol (dotted line). Arrow bars represent one standard deviation [126].

The areas under the misoprostol concentration versus time curve up to 4 hours are 273.3 ± 110 pg x hour/ml orally and 503.3 ± 296.5 pg x hour/ml vaginally and up to 6 hours 300 ± 103.3 pg x hour/ml compared with 956.7 ± 541.7 pg x hour/ml [5].

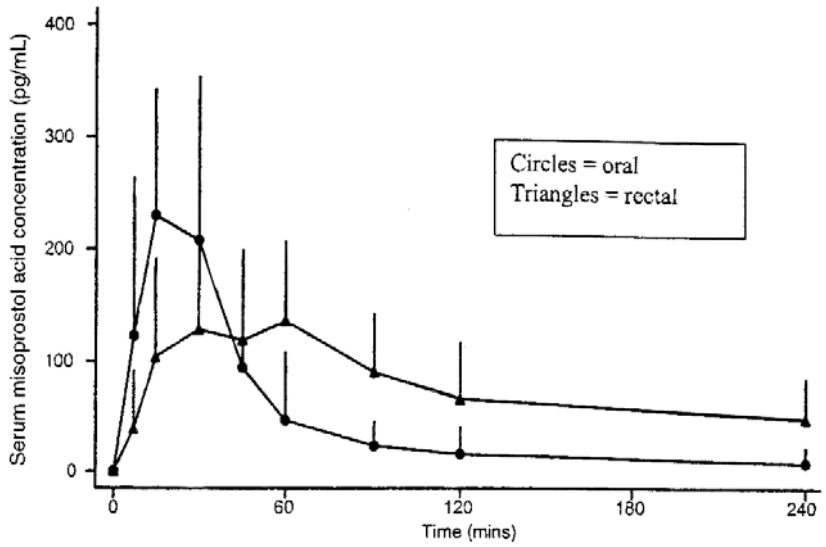

Figure 1-6: Mean plasma concentration of misoprostol acid over time after oral and rectal administration [127].

Khan et al. randomised 20 women into two groups to compare absorption kinetics of orally and rectally administered misoprostol in the third stage of labour. The profile leads to the conclusion that the longer half-life of rectally administered misoprostol might prolong the uterine tonus. This is useful for preventing secondary haemorrhage. Orally administered misoprostol leads to higher peak levels of misoprostol free acid [127].

The same study group showed the absorption of 400 µg rectally, vaginally or orally administered misoprostol in women between 7 and 14 completed weeks of pregnancy. The absorption curves of oral and vaginal misoprostol are similar to the results of Zieman et al. The pharmacokinetic profile of rectally administered misoprostol shows a similarity to that of the vaginal route but with a lower bioavailability [128].

Studying the degree of absorption and uterine contractility after vaginal and oral misoprostol in thirty women with a normal intrauterine pregnancy between 8 and 11 weeks of gestation who requested termination of pregnancy, Danielsson et al. found corresponding activity. The pressure was measured by an intrauterine pressure transducer. After oral misoprostol application of 400 µg the uterine tonus started to increase after a mean of 7.8 ± 3.0 minutes and reached its maximum after 25.5 ± 5.0 minutes. Vaginal misoprostol led to a start of intrauterine pressure after 20.9 ± 5.3 minutes with a maximum after 46.3 ± 20.7 minutes.

The activity was measured in Montevideo units, the product of frequency of contractions per 10 minutes and intraamniotic amplitude of contraction. After application of 200 µg and 400 µg

vaginal misoprostol, the activity increased continuously during the period of 4 hours, as shown in Figure 1-7 and Figure 1-8. This was not observed after oral misoprostol treatment [129]

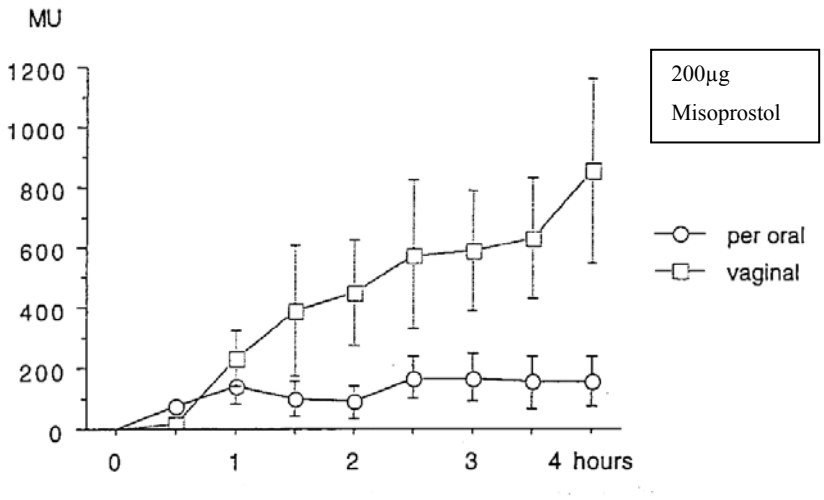

Figure 1-7: Uterine activity in Montevideo units (MU) after oral or vaginal administration of 200 µg misoprostol [130].

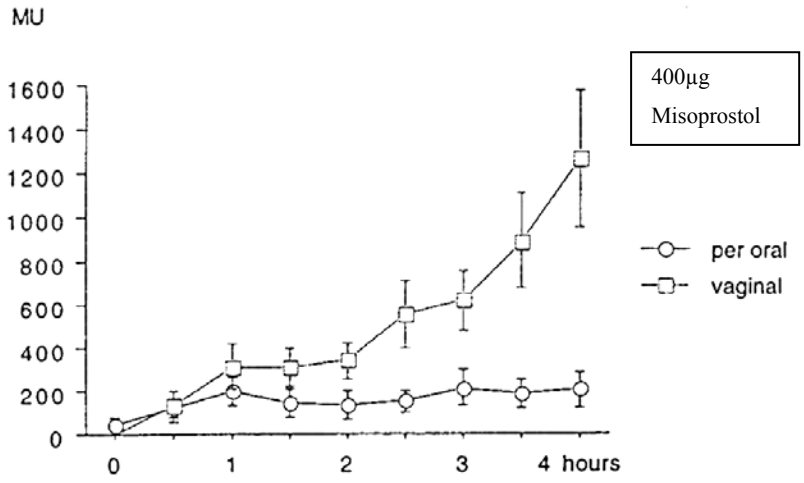

Figure 1-8: Uterine activity in Montevideo units (MU) after oral or vaginal administration of 400 µg misoprostol [130].

The efficacy of vaginal misoprostol application for cervical ripening and labour induction at term does not seem to be influenced by the vaginal pH [121].

The WHO conducted a study on misoprostol's appearance in breast milk, in which 600 µg of misoprostol was given orally during immediate postpartum. One hour after administration the acid reached its maximum concentration of 20.9 pg/ml ± 13.0 pg/ml in colostrum, then declined gradually to <1 pg/ml at 5 hours. The authors concluded that the excreted misoprostol acid might cause shivering, fever and diarrhoea in the breast-fed infant within the following few hours after

administration to the mother. The concentration of misoprostol acid in colostrum per kilogram of body weight, which the newborn might ingest, will be around 7 pg/kg body weight of the newborn (21 pg/3 kg), which is a very small dose [131].

1.6.3 Side Effects and Complications

1.6.3.1 Side Effects

The most common side effects are gastrointestinal side effects such as nausea, vomiting and diarrhoea as well as shivering and pyrexia. In a study of postpartum management of haemorrhage in the first hour after administration of a 600 µg dose of oral misoprostol, El-Refaey et al. noted 8% of the patients with vomiting, 3% with diarrhoea, 62% with shivering and a mean increase of 0.5°C in body temperature [132].
Doses of 1600 µg daily have been tolerated with only mild gastrointestinal discomfort [117].

Misoprostol has a bronchial-relaxing property [133]. Therefore it can be safely used in patients with asthma.

Khan et al. randomised 276 women into three groups for an adverse-effect study in the third stage of labour. Group I received 600 µg misoprostol orally, Groups II and III either 400 µg or 600 µg rectally. Shivering was reported by 76% of the women in Group I, 56% in Group II and 54% in Group III (p=0.003). A temperature rise above 38°C was found in 8 participants in the oral group compared with only three in the two rectal groups combined (p=0.05) [127].

The most worrisome situations in obstetrics are the incidence of abnormal uterine contractile activity, abnormal fetal heart rate tracings and meconium passage. The occurrence though does not lead to neonatal adverse outcomes [134].

Studying the haemodynamic effects of vaginal misoprostol and dinoprostone applied for induction of labour after 41 weeks of pregnancy by measuring the uterine and fetal vascular blood flow by means of Doppler ultrasonography showed that there were no significant changes in the pulsatility index (PI), resistance index (RI) or systolic/diastolic (S/D) ratio in the umbilical artery.
Misoprostol increased the S/D in the uterine artery and PI, RI, S/D ratios in the arcuate artery significantly. The PI and RI of the uterine artery were slightly elevated.

Dinoprostone in comparison caused significant augmentation in all ratios in the uterine and arcuate arteries. These effects may be caused by direct vasoconstrictor effect of prostaglandins. The authors concluded that misoprostol is as safe as dinoprostone for cervical ripening and induction of labour. [135].

1.6.3.2 Previous Cesarean Section and Uterine Rupture

Even though misoprostol is known to cause uterine hyperstimulation some, of the performed studies for induction of labour included patients who had undergone prior cesarean sections or other transmural surgery [136].

In the meta-analysis published by Sanchez-Ramos et al. in 2000, six out of 12 studies on women with scarred uteri reported uterine ruptures. 16 (4.5%) women out of the 355 participants experienced uterine rupture [137].

The incidence of uterine rupture after application of intravaginal misoprostol in the literature varies from 1.4% vs. 0% after oxytocin [138] to 6.25% vs. 1.1% after oxytocin [139] and 5.6% vs. 0.2% without misoprostol [140].

Uterine rupture in a multiparous woman with a previous curettage occurred after four doses of 100 µg oral misoprostol at three-hourly intervals. Examination showed a rupture in the left lateral uterine wall [141].

Wing et al. reported two uterine scar disruptions out of 17 patients who had received multiple doses of 25 µg intravaginal misoprostol; they advise a cautious approach in patients with previous cesarean section [142].

Other studies including women with previous cesarean sections did not note uterine ruptures [143].

The suggestion has been made that misoprostol should not be used routinely in this particular clinical setting [144].

Bennett reported a case of uterine rupture in one woman without prior uterine surgery after two 25 µg doses of intravaginal misoprostol [145].

A similar case report of uterine rupture six hours after insertion of a second 50 µg dose of vaginal misoprostol was published by Thomas and colleagues [146].

Misoprostol has been reported to be safe in grand multiparous women.

These patients were given only one dose of vaginal misoprostol. The women presenting with a viable pregnancy received one dose of 50 µg, those presenting with a late intrauterine death received a 100 µg dose. All women delivered successfully. None of the patients presented with uterine rupture [147].

1.6.3.3 Toxicity

A case report by Bond et al. tells of a woman 31 weeks pregnant who intentionally overdosed ingesting 6000 µg of misoprostol and 8 mg trifluoperazine. She developed hypertonic uterine contractions with fetal death, hyperthermia, tremor, rhabdomyolysis and hypoxemia. She was treated with gastric lavage and administration of activated charcoal. Nine hours after the self administration of misoprostol the symptoms disappeared. It was noted that she had a serum creatine kinase peak level of 5849 U/L 25 hours after ingestion [148].

Another case report of a gravid woman of 36 weeks gestation who ingested 6000 µg of misoprostol vaginally and 600 µg orally, showed almost the same picture. The foetus died before she was delivered by cesarean section [149].

1.6.3.4 Teratogenity

Reports about the possible teratogenity of misoprostol appeared as malformations on children were noted whose mothers had unsuccessfully taken misoprostol for self-induction of abortion during first trimester pregnancy.
Five cases were described with malformation of the frontotemporal region of the skull [150,151].

Another kind of malformation was identified in children whose mothers had undergone an unsuccessful attempt to terminate pregnancy. Out of 42 newborn infants with limb abnormalities, 17 were found with the Möbius syndrome, a congenital cranial paralysis with associated limb defects [152,153]. The deformities found can be attributed to vascular disruption [154].

In 1997, 17 babies were followed up after having been exposed to misoprostol in early pregnancy. No evidence of teratogenity was seen in those cases [155].
Animal studies matched this observation regarding foetotoxic or teratogenic effects [156,157].

The observations mentioned should certainly be considered, though there is no evidence of teratogenity being related to misoprostol.

Today, the reported cases of malformation are rather explained by temporary hypoxia in early pregnancy after the ingestion of misoprostol [2,158].

1.7 Use of Misoprostol in Gynaecology and Obstetrics

1.7.1 Cervical Priming before Diagnostic and Surgical Hysteroscopy

The common complications during hysteroscopy are related mainly to the difficulty of cervical dilatation. The complications include cervical tear, creation of a false track and uterine perforation.

Preutthipan et al. reported that 200 μg vaginal misoprostol 9-10 hours before operative hysteroscopy was effective for preoperative cervical dilatation. The mean dilatation estimated by Hegar dilator was 7.3 ± 0.7 mm as compared with 3.8 ± 1.1 mm after placebo ($p<0.001$). In the misoprostol group, 75.3% needed additional cervical dilatation and 94.9% in the control group ($p=0.001$). Cervical tears appeared in 1.4% after misoprostol and 11.4% after placebo ($p=0.018$). Creation of a false track during dilatation occurred in 1.4% with misoprostol compared with 6.3% with placebo ($p=0.212$). There were two uterine perforations in the placebo group and none in the misoprostol arm ($p=0.497$) [159].

Another study found 400 μg oral misoprostol effective in nulliparous non-pregnant women 12 hours prior to diagnostic hysteroscopy [160].

1.7.2 First Trimester Termination of Pregnancy

1.7.2.1 Cervical Ripening before Curettage

A number of clinical studies have shown that administration of misoprostol before curettage is effective in cervical ripening. Lately, several studies have been performed to determine the optimal dosing regimen of vaginal misoprostol before vacuum aspiration. It was found that a dose of 400 μg administered every 3 hours is an optimal regimen [161-163].

1.7.2.2 Medical Termination

Termination of pregnancies less than eight completed weeks can be achieved in approximately 90% of the patients with misoprostol alone. The mean expulsion time reported was 8.0 ± 3.4 hours with a dosing regimen of 800 μg vaginal misoprostol administered every 24 hours [164].

In combination with either mifepristone or methotrexate, the rate of complete abortion is increased and the required dose of misoprostol is decreased.

Very good results were achieved with oral administration of 200 µg mifepristone followed by 800 µg vaginal misoprostol 36 to 48 hours later. The success rate of complete abortion was 97.5 % [165].
In Berlin, Mund et al. conducted a study of pregnancies up to 49 days post menstruationem applying 400 mg mifepristone orally. 40 hours later the participants self-applied a 600 µg dose misoprostol vaginally. In 5.9% a second misoprostol administration was required as bleeding did not appear within 3 hours. The success rate was 98%. Only 1.85% of the patients had to undergo a curettage [166].
The WHO published data of a multicentre study with a total of 2219 women for termination of pregnancy under 63 days, comparing three misoprostol regimen after mifepristone. The combination of 200 mg mifepristone orally followed by 800 µg misoprostol vaginally after 36-48 hours and continued with 400 µg misoprostol orally twice a day for 7 days resulted in the highest rate of complete abortion with a success rate of 95.0% to 97.8% [167].

A high acceptability of home-used misoprostol by women and their partners was demonstrated in Sweden. Women described that they were more flexible and had more privacy in their abortions [168].

1.7.3 Second Trimester Abortion and Termination of Pregnancy

For mid-trimester abortion misoprostol has proved very effective, too.
Compared with the traditionally used gemeprost, vaginal misoprostol seems to be as effective with less side effects [169,170].
The success rate of complete abortion in women presenting with intrauterine deaths in second trimester of pregnancy seems to be dependent on the gestational age. Women at 17 weeks or more are reported to have a 100% success rate of complete abortion after intravaginal misoprostol whereas those at 13 to 16 weeks only have 67% [171].

A very positive dosing regimen for terminating pregnancy at 12 to 22 weeks gestation was proposed by Jain et al. suggesting a dose of 200 µg intravaginal misoprostol administered every 12 hours. The incidence of abortion within 48 hours was 89.2% and the mean abortion interval was 14 hours. Shortening the dosing interval to six hours produced no significant benefit [172].

Nowadays, mifepristone followed by misoprostol is commonly used in the preparation of second trimester abortion. This regimen is more effective than the combination of mifepristone and gemeprost [173].

Hinshaw et al. prepared the cervix over 36 to 48 hours with 600 µg mifepristone before insertion of the first dose of 800µg misoprostol into the posterior fornix. Subsequent doses of 400µg were administered orally. At 5.75 hours the expulsion time was significantly longer in nulliparous women. All patients aborted within 15 hours [6].

1.7.4 Cervical Ripening and Induction of Labour

The first trial assessing the administration of misoprostol for induction of labour concerned cases presenting with late intrauterine death. 400 µg of oral misoprostol were applied four-hourly. Induction was successful in all the cases [174].

The first study performed in viable pregnancy with misoprostol for the induction of labour was conducted by Margulies et al. in 1991. Vaginal misoprostol was found to be an effective method for third trimester induction of labour with few side-effects on the mother and no apparent adverse effects on the foetus or newborn baby [175].

Interest in misoprostol as an agent for cervical ripening and induction of labour grew. Soon the first study's result was supplemented by several reports about the efficacy and safety of this drug.

1.7.4.1 Vaginal Misoprostol

The first published literature on misoprostol compared intravaginally administered misoprostol to placebo [176], oxytocin [177-179] and other prostaglandin preparations [180-185] for obstetrical use.

Margulies et al. used 50 µg of misoprostol to induce labour in third trimester patients, comparing those at a gestational age of 28 to 36 weeks to those at a gestational age more than 36 weeks. In the first group, 36% of the women delivered within 8 hours whereas in the second group 73% did. These data show a gestational age-dependant response to misoprostol [175].

In 1993, Sanchez-Ramoz et al. compared 50 µg of intravaginally administered misoprostol applied every 4 hours with intravenous oxytocin in patients with an unfavourable cervix.
The investigators confirmed the efficacy and safety of vaginal misoprostol, though they also expressed their concern about the frequency of tachysystole in the misoprostol treatment arm, although the incidence of hyperstimulation syndrome and the rate of surgical deliveries due to fetal distress was not elevated [186].

Fletcher et al. proved that a single misoprostol dose of 100 µg was superior to placebo and as effective as dinoprostone in inducing labour when administered vaginally. There were no differences in delivery outcome in terms of complications [187,188].

The main concern about induction of labour in viable pregnancies with administration of misoprostol, especially through the vaginal route, is the potent uterotonic effect resulting in a high incidence of tachysystole with doses even as low as 50 µg [189].
To assess safety and efficacy, a meta-analysis in the United States involving 966 women was carried out by Sanchez-Ramoz in 1997. Included in the statistical analysis were trials comparing the use of misoprostol for cervical ripening and induction of labour with the use of other prostaglandins, oxytocin and placebo. It revealed that women who received misoprostol had a higher incidence of natural vaginal delivery (NVD) within 24 hours and the time from the start of induction to delivery was reduced by approximately 4.6 hours when compared with control subjects. The cesarean section rate was significantly lower (odds ratio (OR) 0.67, 95% confidence interval (CI) 0.48-0.93) which was explained by misoprostol's ability to effect cervical softening as well as causing adequate uterine activity.
Uterine tachysystole was found mainly in misoprostol-treated groups, the incidence of hyper-stimulation was not raised and clinical intervention for hyperstimulation appeared not to be required more frequently than in control groups.
Comparing the results of 25 µg and 50 µg doses, the 25 µg route showed a decreased incidence of misoprostol-associated tachysystole but an increased induction to delivery interval.
All in all, the analysis confirmed the safety and efficacy of misoprostol [190].

Several studies tried to find the optimal dosing regimen of misoprostol administration.
In 2000 Sanchez-Ramos et al. registered 40 trials in which misoprostol had been administered intravaginally in doses of 25 µg to 200 µg with a frequency of 2 to 6 hours [137].

In search of an optimum dosing regimen for misoprostol, it has been compared with dinoprostone.
In 1995, Wing et al. compared low dose regimen and in 1996 examined different dosing intervals. The outcome measures chosen were an optimum induction to delivery interval and the lowest possible incidence of tachysystole.
The first study compared 50 µg misoprostol tablets every 3 hours with 0.5 mg dinoprostone.

70.6% of the patients in the misoprostol group and 47.8% in the dinoprostone group achieved a vaginal delivery within 24 hours ($p<0.01$). The time from induction to vaginal delivery in misoprostol-treated patients was 15.1 ± 8 hours as compared with 23.5 ± 14.5 hours with those treated with dinoprostone ($p<0.001$). Even though there appeared to be a higher incidence of meconium passage (27.9% vs. 10.5% , $p<0.05$) and a significantly higher rate of tachysystole (36.7% vs. 11.9% , $p<0.001$) with misoprostol, there was no significant difference in intrapartal complications, such as hyperstimulation syndrome, cesarean section rate, or pathological fetal or maternal outcome parameters [189].

In 1996, concerns about contraction abnormalities led to another study testing different dosing intervals by administering 25 µg misoprostol every 3 or 6 hours.
The authors came to the conclusion that the optimum vaginal dose was 25 µg given every three hours. It appears to yield better results regarding the induction to vaginal delivery interval, less oxytocin use, and a reduced rate of failed inductions. The investigation showed one of the lowest incidences of tachysystole in accumulated literature and is comparable with the rate of dinoprostone noted in the comparative study in 1995 [191].

Lately, the preferred doses used were 25 µg and 50 µg of vaginal misoprostol [189,192,193].
However, these regimens were not chosen with reference to pharmacokinetic studies, and other authors argue that a 50 µg dose given 4 to 6-hourly is as safe as the 25 µg dose given 3-hourly.

1.7.4.2 Oral Misoprostol

In the beginning most of the studies experimented with the vaginal administration of misoprostol. Only recently, studies were published assessing the oral administration of misoprostol for cervical ripening and labour induction.
Misoprostol is known to be a potent orally applied active prostaglandin. The question that needed to be addressed next was whether it is effective and safe for inducting labour when taken orally.
Experience about the success of oral misoprostol in first and second trimester abortions suggest that there is a high capacity and wide field for an oral administered agent.

In 1997, Windrim MB et al. conducted a study with 275 women randomised to either 50 µg oral misoprostol 4-hourly or to the established protocol with intracervical or vaginal prostaglandin E_2, amniotomy and oxytocin infusion. The results showed that there were no differences in the mean

time to vaginal birth of approximately 15 hours, in the cesarean section rate or other maternal secondary outcomes. The rates of short term neonatal pathological outcomes were not increased. No women had to be treated with tocolytic agents or cesarean sections for uterine hyperstimulation.
Orally administered misoprostol was confirmed to be an effective and safe agent for induction with minimal gastrointestinal side effects [194].

Another study performed by Toppazada et al. 1997 in Egypt compared oral administration with vaginal administration of misoprostol in unripe cervices. Compared with the prior study, the randomised women received a larger dose of 100 µg either orally or vaginally every 3 hours. The vaginal route was more effective, but showed a much higher incidence of abnormal fetal heart rate tracings even though the total oral dose used was about one-third higher than the complete vaginal dose [195].

Using 50 µg of misoprostol 4-hourly either vaginally or orally in women at term leads to a shorter induction to delivery time of 14.1 ± 6.4 hours with vaginal misoprostol versus 17.9 ± 9.9 hours ($p=0.004$) with oral misoprostol and an increased incidence of tachysystole ($p<0.01$). These results were attributed to the higher bioavailability of vaginally administered misoprostol. The median time to vaginal delivery showed a difference of 2.75 hours, $p=0.38$ [134].
Considering fetal safety oral administration could be seen as an appropriate alternative so far [134,196].
However, the use of misoprostol can be ruled out in general in the case of women with a Bishop score ≥6. In these women oral misoprostol did not offer any benefit over intravenous oxytocin for induction of labour. Oxytocin resulted in a shorter induction to delivery time and was associated with a lower hyperstimulation rate [197].

Lately, the Cochrane database published three trials assessing buccal and sublingual misoprostol for cervical ripening and induction of labour. Both modes of application were as effective as vaginal and oral misoprostol. However, their safety should be evaluated in further studies[198].

1.7.4.3 Prelabour Rupture of Membranes

A group in Hong Kong was the first to use oral misoprostol for inducting labour in patients with prelabour rupture of membranes. To avoid the risk the risk of introducing ascending infection during the application of vaginal prostaglandin preparations, a potent orally administrable drug

seemed to be a desirable approach, especially for patients with prelabour rupture of membranes to reduce the incidence of chorioamnionitis and funisitis.
The patients received either 200 µg oral misoprostol or 50 mg vitamin B6 orally once. The results showed that the oral misoprostol was effective for cervical priming, reducing the need for oxytocin infusion and decreasing the leaking-to-delivery time of 16.2 ± 6.3 hours with placebo to 7.5 ± 6.0 hours (p<0.01). No increase in uterine activity, maternal side effects or perinatal morbidity was noticeable.
The risk of a delayed closure of the foetus`s ductus arteriosus was not observed probably owing to the low dose. The required dose of PGE_1 to keep the ductus open is 0.1 µg/kg per minute.
The conclusion was that route and dose seemed to be effective for cervical ripening and induction of labour in patients with prelabour rupture of membranes [199].

Oral misoprostol at a dose of 75 µg applied every 4 hours was effective, but compared with oxytocin it resulted in a longer induction to delivery time of 164 minutes. The incidence of hyperstimulation was lower in the misoprostol group (6.0% vs. 27.1%) [200].

Frohn et al. described 50 µg intravaginal misoprostol as being more effective than 2.5 mg PGE_2 in treating pre-term rupture of membranes after 34 weeks of gestation. The mean time from induction to delivery was 16.4 hours in the misoprostol group and 22.0 hours in the PGE_2 group, and the percentage of women delivering within 12 hours was 41% after misoprostol versus 16% for PGE_2. Tachysystole occurred in 20% of the women in the misoprostol group and in 6% of the PGE_2 group. The cesarean section rate was 19% with misoprostol as compared with 26% with PGE_2 [201].

1.7.4.4 Intrauterine Death

Several studies of early and late fetal death have been conducted since Mariano-Neto`s study in 1987 [174]. Most of the studies administered doses of 50 µg or 100 µg of vaginal misoprostol. In general, vaginal misoprostol is seen as an effective, safe, low-cost drug, particularly suitable in women of high average parity with a history of late intrauterine deaths [202].
In these cases there is no need to perform fetal surveillance so that the mode of induction most suitable for the woman should be chosen. Oral application of an agent is often preferred by the women for induction of labour with or without viable pregnancy [203].

1.7.5 Therapy of Postpartum Haemorrhage

In case of postpartum haemorrhage, the oral and rectal administration of misoprostol might be a good option.

Chong et al. performed a study measuring intrauterine pressure changes after application of different doses of oral misoprostol (200, 400, 500, 600, 800 µg) compared with intramuscular syntometrine (oxytocin 5 IU and ergometrine maleate 500 µg/ml). There was no statistical difference in the adjusted mean difference in cumulative uterine activity between any of the doses of oral misoprostol on the one hand and intramuscular syntometrine on the other. The mean onset of action in the case of oral misoprostol was significantly slower than in the case of syntometrine (6.1 min vs. 3.2 min, p=0.002). The authors conclude that misoprostol has a definite uterotonic effect on the postpartum uterus comparable to that of syntometrine. The late onset of action may require it to be administered earlier [204].

Bamigboye et al. reported a higher incidence of postpartum diastolic hypertension after syntometrine than in the case of rectal misoprostol in the management of the third stage of labour [205].

In 1997 El-Refaey et al. found that 600 µg oral misoprostol is an effective agent for the prevention of postpartum haemorrhage with a low frequency of adverse events. He suggests that it may be a valuable approach in the postpartum management of pre-eclamptic patients [132].

Misoprostol is reported to be very effective in patients that are unresponsive to conventional first-line management. 1000 µg of rectally administered misoprostol stopped haemorrhage in all women almost immediately [206].

The longer half-life of rectally applied misoprostol might prolong the uterine tonus and prevent secondary haemorrhage as shown in Figure 1-6 on page 19 [127].

Misoprostol can be applied rectally in cases of unconsciousness or general anaesthesia.

The morbidity and mortality in developing countries could be reduced as misoprostol is easy to administer orally and rectally, is stable and does not require special storage [2,132,205,207].