

**THE USE OF MISOPROSTOL IN CERVICAL RIPENING
AND INDUCTION OF LABOUR IN THE TERM
PREGNANCY**

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ABSTRACT

OBJECTIVE: To compare the efficacy and safety of misoprostol (Cytotec) with prostaglandin E₂ (prandin gel) in cervical ripening and induction of labour at term.

STUDY DESIGN: Two independent studies were performed. The first was to evaluate misoprostol as a cervical ripening agent when compared to prandin gel and the second to compare their ability to induce labour.

Two hundred and forty patients requiring cervical ripening prior to induction of labour were recruited to the cervical ripening arm of the trial. Patients were randomly assigned to receive either 100 µg of misoprostol (half a 200 µg tablet) in the posterior fornix or 1mg prandin gel similarly inserted. A Bishop's score of the cervix was performed prior to drug insertion and repeated by the same clinician 24 hours thereafter if labour or delivery had not ensued. If labour commenced it were managed according to standard labour ward protocols.

Three hundred and forty patients who required induction of labour for maternal or fetal reasons at term were recruited to the induction of labour arm of the trial. Half were randomly allocated to receive 100 µg misoprostol (half a 200 µg tablet) in the posterior fornix and half, 1mg prandin gel in the posterior fornix. If after 4 hours the labour had not ensued or the cervix remained too unfavourable for amniotomy, then a second dose of the drug was used. Labour and delivery was managed according to standard labour ward protocols.

RESULTS: In the cervical ripening trial, data was analysed on 113 patients in the misoprostol arm and 116 in the prandin arm. The demographic characteristics were similar in both groups. Significantly more patients delivered within the 24 hour ripening period with misoprostol (88 (77.9%)) than with prandin gel (47 (40.5%)) (P < 0.001). In those patients delivered within 24 hours, the induction of labour to delivery interval was similar

at, 9 hours 30 minutes (SD = 5h30) for misoprostol and 10 hours 51 minutes (SD = 5h09), with prandin gel. Significantly more patients in the prandin gel arm required oxytocin augmentation (25.5% versus 12.5% with misoprostol) but the caesarean section rate (13.6% with misoprostol and 12.7% with prandin gel) and analgesic usage were similar. Maternal side effects were similar in the two groups but tachysystole was significantly more common at 12.4% with misoprostol and 1.7% with prandin gel ($P < 0.01$). In those patients undelivered at 24 hours, there was a significant improvement in the number of patients with a Bishop's score of > 4 with both drugs. Neonatal outcomes, including Apgar score and admission to the neonatal intensive care unit were not significantly different.

In the induction of labour arm of the trial the demographic characteristics of both groups were similar. The use of misoprostol resulted in a significantly higher number of patients delivering within 12 hours of drug insertion than with prandin gel (136 (80%) with misoprostol versus 91 (66,9%) with prandin gel, $P < 0.001$). There was also a significantly shorter insertion to delivery interval with misoprostol (9hr13 (SD = 5hr 53)) than with prandin gel (12hr18 (SD = 6h22)), ($P < 0.001$). Thirty nine patients in the misoprostol group required a second dose of the drug versus 55 patients in the prandin gel group ($P < 0.05$). Although the caesarean section rate was similar with the two drugs (30.6% with misoprostol and 34.1% with prandin gel) significantly more patients had a caesarean section for fetal distress in the misoprostol group (21.8% vs 10.6%) ($P < 0.05$). Neonatal outcome, as assessed by Apgar score and admission to the neonatal intensive care unit, was however not different with either drug. Four patients had abruptio placentae in the misoprostol group and the incidence of tachysystole was significantly higher at 28.2% vs 15.3% with prandin gel ($P < 0.01$). Oxytocin was used for labour augmentation in 52.9% of patients with prandin gel and 27% with misoprostol ($P < 0.05$). Analgesic usage and other maternal side effects were similar with both drugs.

CONCLUSION: Misoprostol is an effective cervical ripening and induction of labour agent when compared to prandin gel. However it results in a higher incidence of

tachysystole, caesarean section for fetal distress and abruption placentae and cannot yet be recommended for general use until the concern over adverse fetal and maternal outcome is addressed in larger trials.

INTRODUCTION

Delivery of the fetus is often indicated for maternal or fetal reasons prior to the spontaneous onset of labour. Various methods have been used to induce labour with the aim to bring about delivery via a method as physiological as possible that does not harm mother or fetus.

Historically, various herbs such as juniper, cinnamon, pennyroyal and mugwort were used, as were various forms of forced mechanical dilation of the cervix (Thiery et al, 1990). These methods often resulted in fetal damage or demise and severe consequences for the mother, such as of infection, haemorrhage and even death. As medicine and science have advanced, more has become known about the physiology of normal labour and with this, new pharmacological agents have been developed for the induction of labour. Currently three major groups of agents are used to initiate labour in clinical practice. These are the prostaglandins, hydrophilic cervical dilators and oxytocin (used in conjunction with artificial rupture of membranes). The prostaglandins appear to be the most effective agents acting with the dual action of ripening the cervix and stimulating uterine contractions (Keirse, 1994a; Keirse, 1994b).

With the use of prostaglandins successful induction of labour is achieved in 30% to 80% of patients (Keirse, 1994b). Adverse side effects of these drugs include gastrointestinal symptoms, pyrexia and uterine hyperstimulation (Reynolds, 1996). A high proportion of these patients also require augmentation with oxytocin which carries with it added potential complications and side effects (Keirse, 1994b). The most commonly used prostaglandin is prostaglandin E₂ used either intravaginally or intracervically. It is however, an expensive drug and requires continuous refrigeration. As a consequence of these factors clinicians have continued to seek more effective, safer and cheaper agents for induction of labour.

In the early 1990's it emerged that misoprostol, a prostaglandin E₁ methyl analogue, was being used extensively in Brazil as an illegal abortifacient (Schönhöffer, 1991; Costa and Vessey, 1993; Coelho et al, 1993). Misoprostol, marketed by Searle as a

gastric mucosal protector, appeared to ripen the cervix and induce uterine contractions if taken orally or placed intravaginally. Scientific evaluation followed, and a number of studies have reported on its use in first and second trimester abortions (Norman et al, 1991; Baird et al, 1992; Jain and Mishell, 1994; Bughalo et al, 1993). It appears to be an effective cervical ripening agent and is used as an adjunct to the anti-progesterone mifepristone (RU486) (Norman et al, 1991; Baird et al, 1992; Peyron et al, 1993; Mckinley et al, 1993; El-Refaeily and Templeton, 1994) or to manual evacuation (El-Refaeily et al, 1994; Bughalo et al, 1994a; Ngai et al, 1995). Initial studies on its use in the third trimester, in viable pregnancies, suggested that it may be an effective and safe cervical ripening and induction of labour agent (Fletcher et al, 1993; Sanchez-Ramos et al, 1993; Fletcher et al, 1994; Wing et al 1995a; Wing et al 1995b).

These trials suggested significant potential advantages of the drug over other commonly used agents. As a consequence further clarification was needed as to its efficacy and safety in clinical practise. It was with these considerations that the following clinical trials were conducted.

This thesis will present and discuss the results of two clinical trials comparing the efficacy and safety of misoprostol (Cytotec) and prostaglandin E₂ (Prandin gel) in cervical ripening and induction of labour at term. The physiological changes associated with the onset of labour and its hormonal and endocrine initiators will be discussed, as will our current understanding of the pharmacology and clinical effectiveness of misoprostol.

CHAPTER 1

LITERATURE REVIEW

1.1. PHYSIOLOGY OF NORMAL LABOUR

In order to appropriately evaluate methods of induction of labour (IOL) it is important to understand the natural physiology of labour onset.

The hormonal and endocrine changes that precede labour begin at approximately 34 to 36 weeks and result in gradual ripening of the cervix and an alteration in myometrial activity over the last 4 to 6 weeks of pregnancy. These changes culminate in the onset of progressively stronger and more frequent contractions and dilatation of the cervix, leading to delivery of the fetus.

1.1.1 ENDOCRINE CONTROL

In a number of animal models the full sequence of endocrine events culminating in the initiation of labour and delivery have been fully elucidated. This is not true of human pregnancy. Firstly, the fetus in late pregnancy is relatively inaccessible and secondly, there are a number of technical difficulties associated with the investigation of the endocrine initiators of labour (Turnbull, 1989). A number of the hormonal effects associated with the onset of labour are paracrine rather than endocrine in nature and circulating blood levels may thus not be altered. The extended time scale of hormonal and endocrine changes, also makes the determination of their role more difficult.

It appears that the key players in the onset of human labour are the locally released prostaglandins. Oestrogen, progesterone and cortisol play important roles but are not the critical initiators described in other animal models. Oxytocin plays a permissive function in onset of labour and then is involved in maintenance and progression of contractions.

PROSTAGLANDINS

Prostaglandin E₂ (PGE₂) has been shown to stimulate the enzymatic breakdown of collagen fibres (Uldbjerg, 1989; Hayashi, 1993), activate fibrocytes (Calder and Greer, 1992) and increase tissue fluid in the cervix (Ellwood et al, 1980). These are all factors important in cervical ripening. The prostaglandins also influence the formation of myometrial gap junctions (Garfield et al, 1980). These are low resistance pathways allowing the flow of excitation in the uterine muscle, necessary for efficient and co-ordinate uterine action. Prostaglandins also directly stimulate myometrial contractions (Huszar and Walsh, 1991).

Both PGE₂ and PGF_{2α} are released locally by the uterine tissues and exhibit a paracrine effect. They are rapidly cleared from the systemic circulation by the lungs. Prostaglandin FM (PGFM), a breakdown product of PGF, is longer lasting however and can be more readily detected in maternal serum.

The amnion and chorion have the ability to produce PGE₂ and the decidua both PGE₂ and PGF_{2α}. Pregnancy is maintained through the inhibition of this prostaglandin synthesis within the intrauterine tissues, particularly the decidua. This inhibition emanates locally and may also arise from the conceptus (Casey and MacDonald, 1986). Two proteins have been identified from amniotic fluid that have been shown to inhibit prostaglandin synthesis (Wilson et al, 1985; Mortimer et al, 1985). This inhibition is particularly effective in early pregnancy but decreases as pregnancy advances (Casey and MacDonald, 1986).

As the end of gestation draws nearer it is probably a fetal signal, perhaps passed via the fetal urine that stimulates the amnion to produce PGE₂ and releases the decidual inhibition, leading to the production of PGE₂ and PGF_{2α} (Strickland et al, 1983). This signal acts by increasing the release of the prostaglandin substrate arachidonic acid from glycerophospholipids in the amnion and by increasing the activity of prostaglandin synthetase (Casey and MacDonald, 1986). Although serum levels of

PGE₂ and PGF_{2α} have not been shown to be raised in labour (Mitchell et al 1978), serum PGFM is markedly elevated (Sellers et al, 1981; Fuchs et al, 1983). Amniotic fluid levels of PGE₂ and PGF_{2α} are also significantly raised in labour (Keirse et al, 1974). A number of other indirect measures support the high levels of both PGE₂ and PGF_{2α} in labour. Stimuli known to cause the release of prostaglandins such as cervical manipulation and stripping and rupture of the membranes, augment and induce labour (Mitchell et al 1977; McColgin et al, 1993). Fetal breathing movements known to be suppressed by prostaglandins also cease 48 to 72 hours before the onset of labour (Castle and Turnbull 1983).

The maintenance of these levels of PGE₂ and PGF_{2α} in labour results from both the ongoing availability of free arachidonic acid as a substrate for prostaglandin production as well as the absence of the prostaglandin metabolising enzyme, prostaglandin dehydrogenase, in the amnion (Turnbull, 1989).

Prostaglandins also appear to be important in the third stage of labour. Sellars and co-workers (1982) noted peak PGFM levels five minutes after delivery.

CORTISOL

The role of the fetal adrenal in human labour is not clear. In sheep, fetal cortisol is the hormonal trigger of labour (Bassett and Thorburn, 1969). Cortisol induces induction of placental enzymes and hence changes hormonal production, notably reducing progesterone (Anderson et al, 1975) and increasing oestrogen and PGF (Turnbull, 1989).

Cortisol has been shown to be raised in the amniotic fluid in late pregnancy in humans (Murphey et al, 1975; Fencl and Tulchinsky, 1975). However cortisol levels just prior to and after the onset of labour are equal, suggesting no particular surge to be responsible for the initiation of labour (Turnbull, 1989). High doses of potent corticosteroids in late pregnancy also fail to induce labour (Turnbull, 1989).

OESTROGEN

The fetal adrenal has been shown to play a role via its effect on placental oestrogen production. Increased production of dehydroepiandrosterone sulphate (DHEAS) in the fetal adrenal in late pregnancy provides a placental substrate for 17β -oestradiol production. Oestrogen, produced by the membranes and decidua rises after 34 to 35 weeks (Darne et al, 1987; Lewis et al 1987). Although there is no acute rise in prelabour oestrogen levels it is thought necessary that a critical concentration be reached to facilitate labour initiation (Davidson et al, 1987). Oestrogen plays an important role in stimulating prostaglandin production in the amnion, chorion and decidua (Speroff, 1989). It is also involved in cervical ripening (Calder and Greer, 1992), myometrial gap junction formation (Garfield et al, 1980), the enhancement of rhythmic uterine contractions and in the uterus's responsiveness to oxytocin (Fuchs et al, 1982).

PROGESTERONE

Progesterone withdrawal is thought to be important in the onset of labour. A reduction in progesterone levels decreases the resting potential of the myometrium (Garfield et al, 1980) as well as increasing the response of the uterus to electric and oxytocic stimuli (Garfield et al, 1980). Reduced levels also promote cervical ripening by releasing the progesterone inhibition on cervical collagenase activity and neutrophil influx into the cervix (Calder and Greer, 1992). Progesterone inhibitors given in adequate doses can induce abortion (Bygdeman and Van Look, 1988) and pharmacological treatment with progesterone has been shown to suppress preterm labour (Femini et al, 1985; Erny, 1986). However conflicting evidence exists whether serum progesterone levels fall or if only withdrawal at a local level is necessary for the stimulation of labour (Caspo et al 1971; Turnbull et al, 1974; Darne et al, 1987; Lewis et al 1987).

OXYTOCIN

Oxytocin released by the posterior pituitary stimulates the uterus to contract causing both expulsive forces on the fetus and traction on the cervix. The Ferguson reflex, a neuro-efferent pathway from the dilating cervix, maintains oxytocin release by the posterior pituitary resulting in ongoing uterine contractions (Flint et al, 1975). Endogenous oxytocin levels remain constant throughout pregnancy as well as early and late labour (Dawood et al 1978; Sellers et al, 1981b). There are however significant increases in oxytocin receptors and consequently an increased sensitivity of the uterus to oxytocin in late pregnancy and labour (Fuchs et al, 1982). Raised oestrogen and prostaglandin levels in late pregnancy increase the myometrial responsiveness to oxytocin (Turnbull, 1989) and in a self perpetuating fashion oxytocin stimulates decidual cells to release prostaglandins (Fuchs et al, 1981; Wilson et al 1988).

RELAXIN

Although this paracrine hormone appears to be involved in parturition, its specific role is yet to be clearly delineated. Relaxin is derived from the decidua and/or amnion and is thought to inhibit myometrial contractility (Huszar and Walsh, 1991) and prevent amniotic production of PGE₂ until late pregnancy (Lopez-Bernal et al, 1987). With spontaneous labour it promotes prostaglandin production, connective tissue remodelling and cervical ripening (Lopez-Bernal et al, 1987).

1.2.1 CERVICAL RIPENING

Changes in the compliance of the cervix are important in the onset and outcome of labour (Olah, 1995). Softening, increased elasticity and dilation of the cervix are all essential for vaginal delivery. These are brought about mainly by changes in the connective tissue element of this fibromuscular structure.

There is a gradual decrease in the total collagen of the cervix as pregnancy advances. This has been shown both histologically (Junqueira et al, 1980; Elkman et al, 1986) and by falling hydroxyproline levels (Junqueira et al, 1980; Uldberg et al, 1983; Granström et al 1989). By term the amount of collagen reaches 30% to 40% of that of the non pregnant state (Uldberg et al, 1983). An associated increase in soluble collagen, a degradation product of collagen breakdown, suggests that this is probably due mostly to degradation of pre-existing collagen (Junqueira et al, 1980; Kleissl et al, 1978)

Collagenolytic activity has been shown to increase as much as 10 to 14 fold in the cervix prior to and during labour (Uldberg et al, 1983; Rajabi et al, 1988). Granström and co-workers (1992) have shown that not only is the collagenase activity increased at term but that in patients with ripe cervixes it is significantly higher than their non-ripe counterparts. Higher levels of serum collagenases have also been shown in patients in preterm labour with cervical dilatation (Rajabi et al, 1987). There however appears to be no correlation between collagenase activity and degree of cervical dilation or duration of labour (Granström et al, 1992; Uldberg et al, 1983).

Granström and co-workers (1992) have suggested that cervical ripening takes place in several stages. The first being a prolonged early stage where there is a reduced accumulation of collagen relative to non-collagenous components and a slow increasing turnover of collagen. Then a second stage of rapid collagenolytic activity in the pre-labour period and in the latent phase (1cm to 4cm dilatation) as preparation for active labour.

In the non pregnant state the predominant cell type within the cervix is the fibroblast (Junqueira et al, 1980). As pregnancy advances there is an influx of mast cells, macrophages and a high concentrations of neutrophilic polymorphonuclear leucocytes (PMNL) (Junqueira et al, 1980). Polymorphonuclear leucocytes are known to secrete collagenases and that causes collagenolysis. Electron micrographs have shown degranulation of these leucocytes within areas of the cervix that are also clear of collagen (Junqueire et al, 1980). Polymorphonuclear leucocyte infiltration and collagenolysis occur throughout pregnancy but accelerate prior to and during labour (Junqueire et al, 1980).

There is also considerable reorganisation of the collagen fibres as measured by X ray diffraction (Aspeden, 1988), optical and electron microscopy (Junqueira et al, 1980), and collagen solubility (Uldberg et al, 1983; Osmers et al, 1990; Granström 1991). The collagen fibril bundles become disarrayed, with variability in orientation, size and diameter of the fibrils.

Alteration in the cervical ground substance occurs with cervical ripening but the importance of these changes are not as clear as the changes in the collagen. Uldberg and co-workers (1983) have shown a significant increase in the water concentration in the human cervix at term. A decrease in the concentration of sulphated glycosaminoglycans and hyaluronic acid has also been noted (Uldbjerg et al, 1983). There is also a two to five fold increased turnover of proteoglycans, resulting in an altered proteoglycan pattern in the tissues and a change in their relation to the collagen content (Norman et al, 1991). This may explain the change in collagen arrangement noted by other authors above.

These changes in the structure of the connective tissue are not restricted to the cervix but also occur in the connective tissue of the uterine fundus and isthmus (Granström et al, 1989).

The factors regulating uterine connective tissue remodelling are not well understood. Prostaglandins are produced in the cervix and their levels increase at the onset of

cervical ripening (Ellwood et al, 1980). Biochemical evaluation has suggested that they increase the collagenolytic activity in the cervix and reduce the collagen concentration (Uldbjerg, 1989; Hayashi R, 1993; Rajabi et al, 1992). They also affect the glycoprotein composition of the ground substance (Uldbjerg and Ulmsten, 1990).

Oestrogens stimulate collagenase production by cultured cervical tissue (Rajabi et al, 1992) and intravenous DHEAS converted to 17β -oestradiol in the placenta has a similar effect (Mochizuki et al, 1978). Oestrogens also induce prostaglandin synthesis and are thought to sensitise the cervix to the action of prostaglandins (Uldbjerg and Ulmsten, 1990).

Progesterone exerts an inhibitory role on cervical ripening. It is both inhibitory of collagenase production (Rajabi et al, 1988) and prevents influx and activation of neutrophils in the cervix (Calder and Greer, 1992). Progesterone blocking agents have been shown to alter collagen fibre arrangement and increase the cellular content of cervical tissue (Hegele-Hartung et al, 1989). In in-vitro studies of endometrial stromal cells, progesterone antagonists also stimulate endogenous $\text{PGF}_{2\alpha}$ production and inhibit its catabolism (Kelly et al, 1986).

The effect of relaxin on the human cervix is not clear but in rats it stimulates collagen breakdown and increases the concentration of dermatan sulphate and hyaluronic acid (Downing and Sherwood, 1986).

Regulatory substances such as cytokines, TGF- β and interleukin-1 produced by inflammatory cells (macrophages, neutrophils, mast cells and eosinophils) probably also play an active role in controlling the remodelling of the uterine cervix (Granström et al, 1991; Junqueira et al, 1980).

1.1.3 MYOMETRIAL CONTRACTIONS

There is a functional interrelationship between the myometrium and cervix. They act synergistically to contain the uterine contents during pregnancy and then to expel them at term.

The myometrial smooth muscle cells are distributed in an extracellular matrix made up mostly of collagen fibres. This facilitates the transmission of contractile forces by individual muscle cells. The muscle cells communicate with one another via gap junctions. These are believed to synchronise the myometrial contraction through conduction of electrophysiological stimuli during labour (Garfield et al, 1978) There are few such junctions in early pregnancy but their numbers increase as gestation progresses (Garfield et al, 1982). Oestrogens, progesterones and prostaglandins all have regulatory roles in the formation and function of these gap junctions (Garfield et al, 1980).

The current understanding of the mechanism of myometrial smooth muscle cell contraction is well described by various reviewers (Egarter and Husslein, 1991; Carsten and Miller, 1987; Huszar and Walsh, 1991). It is similar to that of skeletal muscle, and is based on the sliding of actin and myosin filaments over one another. The sliding action is initiated by the formation of cross-bridges between the myosin heads and the actin monomers. This is followed by conformational changes in the myosin head that causes the myosin filament to move over the actin filament. The actin-myosin interaction is regulated via enzymatic phosphorylation and dephosphorylation of the myosin light chain on the myosin filament. The phosphorylation required for contraction is dependant on the action of myosin light chain kinase (MLCK) and the dephosphorylation on myosin light chain phosphatase.

The action of MLCK is in turn dependant on three intracellular regulatory factors viz. intracellular free calcium levels, secondly, the formation of a Calcium-calmodulin complex that forms with the influx of calcium into the cell and thirdly, cyclic AMP (cAMP). The former two are permissive while cAMP inhibits contraction via the

stimulation of MLCK phosphorylation and the activation of calcium pump returning calcium to the sarcoplasmic reticulum. Figure 1.1 illustrates the interaction of these intracellular regulatory systems. The control of these events involves oestrogen, progesterone, oxytocin, prostaglandins, relaxin and α and β adrenergic stimulation.

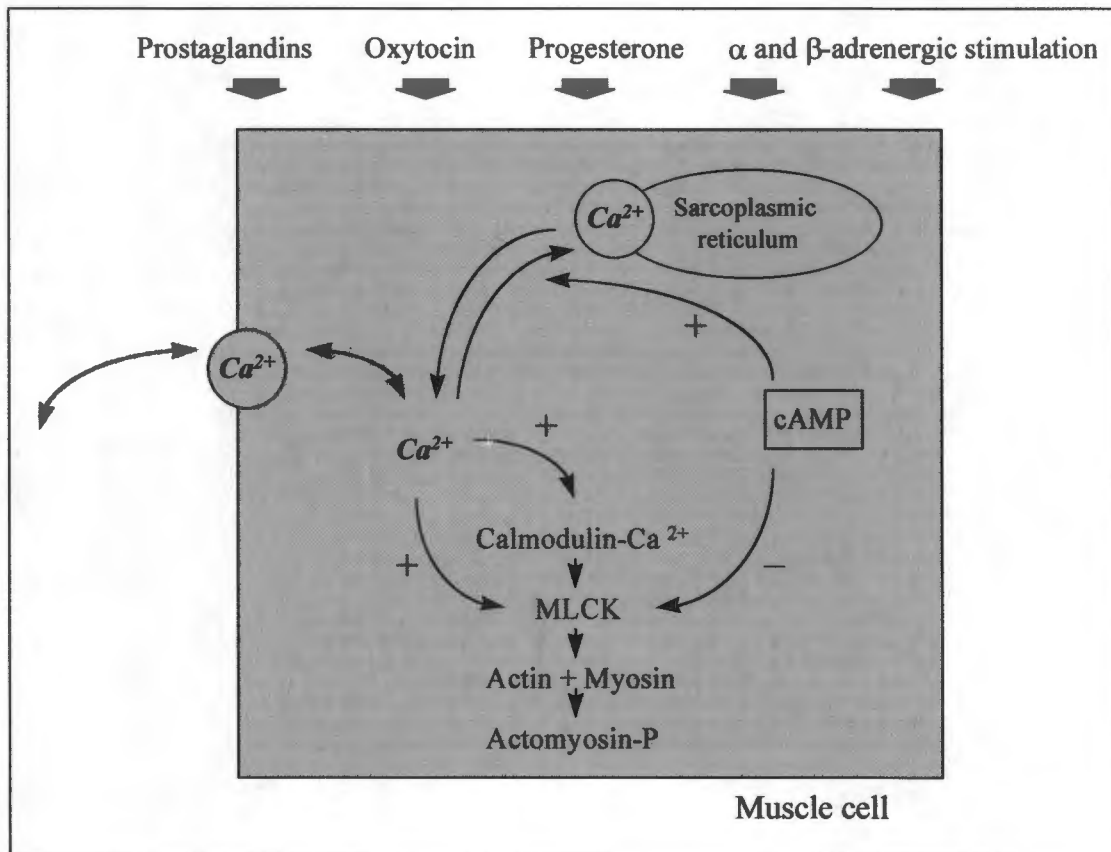


Figure 1.1 The control of the contractile elements within the uterine smooth muscle cell. The action of MLCK is regulated through intracellular calcium and cAMP levels.

Prostaglandins cause myometrial contraction and it has been suggested that the increased synthesis of PGE_2 is the key event in the onset of regular contractions (Strickland et al, 1983). The prostaglandins act via their effect on calcium flux into the myometrial cell (Ohanishi and Devlin, 1979). The exact mechanism is uncertain but PGE_2 and $PGF_{2\alpha}$ increase the cell membrane permeability to calcium and also act as

calcium ionophores. Their action is mediated via specific receptors located on the plasma membranes of target cells. There is regional sensitivity of the uterus to the various prostaglandins which may reflect the influence of other mediators, such as α and β adrenergic innervation (Huszar and Walsh, 1991). Figure 1.2 shows a schematic representation of the effect of prostaglandins, steroids and catecholamines that influence myometrial action.

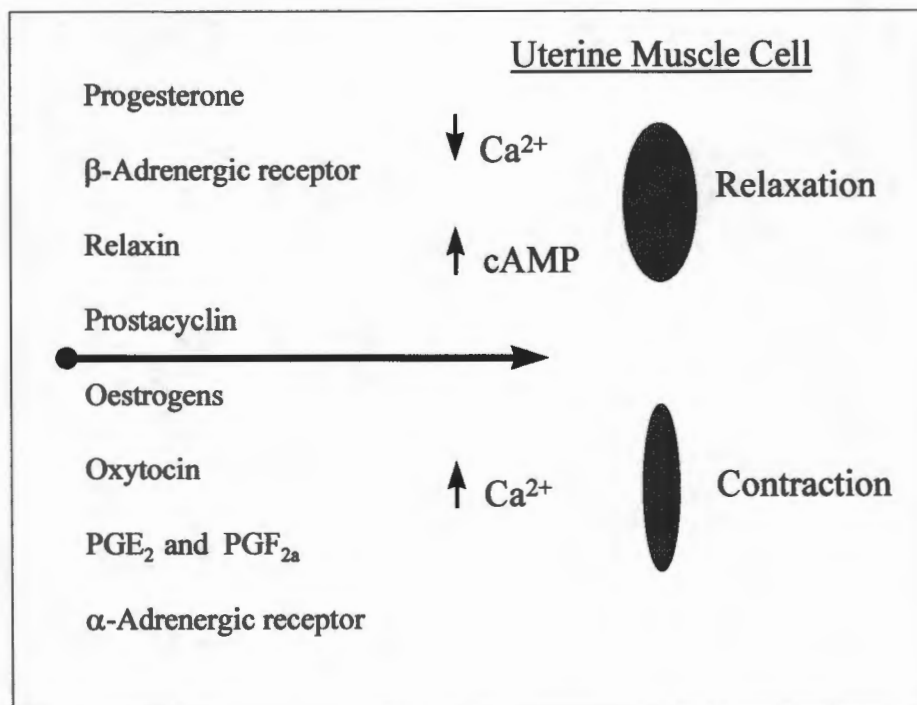


Figure 1.2 Schematic representation of the prostaglandin, steroid and catecholamine effects on the uterine smooth muscle cell.

Progesterone acts on the myometrial cell resulting in reduced cell membrane permeability to calcium. Progesterone also modulates intracellular calcium binding making less calcium available for the calmodulin-MLCK system (Egarter and Husslein, 1991). Both actions reduce contractility and maintain uterine quiescence. Progesterone also attenuates prostaglandin biosynthesis (Egarter and Husslein, 1991). Indirect clinical evidence suggests that progesterone stimulates β adrenergic receptors leading to the preponderance of prostacyclin synthase. This together with progesterone stimulation of cAMP causes the relaxation of smooth muscle cells. Oestrogens have the opposite effect, they stimulate the formation of α -adrenergic receptors (stimulating

a decrease in cAMP levels) and lead to an increased production of $\text{PGF}_{2\alpha}$ (Egarter and Husslein, 1991).

It is postulated that oxytocin has a dual mechanism leading to uterine contractions. Oxytocin, bound to its receptor inhibits Ca^{2+} ATPase on the myometrial cell membrane as well as on the endoplasmic reticulum resulting in an influx of calcium from both these areas into the intracellular area (Huszar and Walsh, 1991). Oxytocin may also increase prostaglandin synthesis in the decidual tissues (Fuchs et al, 1981; Wilson et al 1988).

Relaxin decreases myometrial contractility. It acts via decreasing intracellular calcium levels and MLCK activity (Huszar and Walsh, 1991). It however does not appear to affect contractions induced by oxytocin or prostaglandins. Hence its role appears to be one of inhibiting spontaneous contractility in pregnancy but enhancing cervical ripening at term without interfering with the uterine contractions of labour (Lopez-Bernal et al, 1987).

Adrenergic receptors have been identified in the myometrium and have been shown to affect uterine contraction (Huszar and Walsh, 1991). α -Adrenergic stimulation causes uterine contraction and β -adrenergic stimulation causes relaxation. Receptor concentrations alter through pregnancy as does their distribution in the myometrium. There also appears to be variation in individual response to adrenergic stimulation. Their action on uterine function is influenced by other steroid regulatory pathways.

1.2 METHODS OF CERVICAL RIPENING AND INDUCTION OF LABOUR

The increasing understanding of the endocrine initiators of labour and the physiological changes that occur in the uterus and cervix, has facilitated the development of pharmacological agents for labour induction. The efficacy of the agents is varied, as is their side effect profiles, ease of use and patient acceptability.

As has been discussed earlier, the spontaneous initiation of labour is a continuum of cervical ripening and maturation of uterine activity that begins in the last four to six weeks of pregnancy. If induction of labour is attempted early in this pre-labour period, it is likely to be difficult, prolonged and associated with complications (Keirse and van Oppen, 1990). The ripeness of the cervix is one of the main indicators of potential success of induction of labour (Bishop, 1964; Granström et al, 1991). Consequently, induction of labour agents can be divided into two categories; those that are primarily used to ripen the cervix (in order to facilitate subsequent induction of labour) and those that are used specifically to induce labour. There is obviously a large overlap in these two areas.

1.2.1 CERVICAL RIPENING

Currently the most successful agents for pre-labour cervical ripening are the prostaglandins. Keirse, in a meta analysis of the literature from 1971 to 1990 was able to show the odds of improving cervical ripeness with prostaglandins, when compared to placebo, was 80% to 90% (Keirse, 1993 and references therein). The use of prostaglandins also resulted in a significantly higher incidence of patients going into labour and delivering during the ripening period. Their use, however, is associated with a 5,3% incidence of uterine hyperstimulation and an increase in fetal heart rate abnormalities. This however does not result in a higher caesarean section rate or more adverse fetal outcome.

The two most commonly used routes of administration of prostaglandins are intravaginal and intracervical. Neither route has been shown to be superior over the other (Keirse, 1993 and references therein). Oral administration, has however, been shown to be unsuitable for cervical ripening as repeated doses over long periods of time are required for effectiveness.

Most research has been performed using PGE₂. Prostaglandin F_{2α} has been compared to placebo and has been shown to be effective in cervical ripening (Keirse, 1993 and references therein). Meta-analysis of the trials directly comparing PGE₂ and PGF_{2α} has shown that neither prostaglandin is significantly superior to the other in cervical ripening. Higher doses of PGF_{2α} are however needed and side effects, including uterine hyperstimulation are more common.

Other agents have been used for cervical ripening but with less success than the prostaglandins. Mechanical cervical dilators, made from either sterilised *laminaria japonica* (a type of seaweed) or synthetic substances with similar hygroscopic properties, have been used. The principle behind their effectiveness is the stimulation of prostaglandin release as they expand and stretch the cervix (Uldbjerg and Ulmsten, 1990). Trials have shown them to be safe and to both increase the Bishop's score of the cervix, as well as to increase the proportion of women who deliver vaginally within 12 hours of their use (Cross and Pitkin, 1978; Lackritz et al, 1979).

Other hormones and their precursors have been used in cervical ripening. They have shown varying degrees of efficacy but have not been widely adopted into clinical practise. Intravenous 17 β-oestradiol and cervically applied oestrogen have both been shown to induce cervical ripening at term (Pinto et al, 1965; Gordon and Calder, 1977). Dehydroepiandrosterone sulphate given intravenously also increases cervical collagenolytic activity and cervical ripeness (Mochizuki et al, 1978; Sasaki et al 1982). This is probably via its conversion to 17 β-oestradiol in the placenta and hence the effect of oestrogen on the cervix. Relaxin has been used clinically for cervical ripening at term and has been shown to improve the cervical score within 12 hours following vaginal application (MacLennan et al, 1980; Evans et al, 1983).

Oxytocin has been investigated as a cervical ripening agent. It however shows no superiority over placebo in cervical ripening and the authors of a large meta-analysis on the subject recommend that its use for this indication be abandoned (Keirse and van Oppen, 1990a).

1.2.2 INDUCTION OF LABOUR

In induction of labour, the prostaglandins have been shown to be more effective than placebo. A meta analysis of the literature from 1971 to 1990 by Keirse, showed that the use of prostaglandins improved the odds of a successful induction of labour by 80% to 90 % over placebo (Keirse, 1994b and references therein). Prostaglandins increased the number of patients delivering within 12, 24 and 48 hours of induction of labour. They also reduce the number of patients needing a second induction attempt, as well as the overall caesarean section rate. No increase in adverse perinatal outcome is noted.

Prostaglandins are however associated with side effects. These are to a degree dependant on the route of administration and the doses given (Keirse, 1994b and references therein). Gastrointestinal symptoms such as nausea, vomiting and diarrhoea are reported in between 5% and 20% of patients. Uterine hyperstimulation is also a described complication with prostaglandins. Pyrexia, resulting from the direct stimulation of the thermoregulatory centres in the brain is also reported. Side effects occur least with vaginal and intracervical PGE₂ administration, and with doses ranging from 0.5 mg to 3g.

Prostaglandin F_{2α} is less commonly used in induction of labour than PGE₂. This is because, in order to get similar efficacy with PGF_{2α}, doses 8 to 10 times higher are required (Keirse and Chalmers, 1990). These higher doses are associated with a significant increase in gastrointestinal and thermoregulatory side effects.

Probably the most common method of induction of labour remains the use of oxytocin together with artificial rupture of membranes. The polypeptide hormone, oxytocin has been synthesised commercially for over 30 years. Used alone for induction of labour it is not as effective as when combined with amniotomy (Keirse and van Oppen, 1990b). Intravenous administration is the route of choice for oxytocin. This allows for titration of dosage according to patient sensitivity. Various dosage schedules are used but few formal comparisons of their efficacy have been made.

Oxytocin usage has a number of disadvantages. Oxytocin's inherent anti-diuretic hormone effect, combined with its need for titration in fluid, place the patient at risk of water intoxication and the manifestations of convulsions, coma and death (Schwartz and Jones, 1978). As with most of the induction agents there is also the risk of uterine hyperstimulation and tachysystole, which may result in reduced fetal oxygenation and the sequelae thereof (Keirse and van Oppen, 1990b). If used injudiciously in the face of cephalopelvic disproportion, oxytocin stimulation can result in uterine rupture. Its use has also been associated with a higher incidence of neonatal jaundice for which the reason is still unclear (Friedman et al, 1976; D'Souza et al, 1979).

Comparing prostaglandins to oxytocin (with amniotomy) it appears that the prostaglandins are superior in achieving a vaginal delivery (Keirse and van Oppen 1990b). The proportion of patients undelivered at 12 hours post induction is similar, but with prostaglandins the proportion undelivered after 24 and 48 hours is significantly less. However perinatal outcomes are similar except for the increase in neonatal hyperbilirubinaemia with prostaglandins. The side effects of gastrointestinal disturbances and pyrexia are also more common with the prostaglandins than oxytocin.

Favouring the use of prostaglandins is a high patient acceptance and the perception that they appear to result in a labour more akin to natural labour. (Kennedy 1982).

Amniotomy as a means of inducing labour has been in clinical practise for over 200 years (Calder, 1983). Its effectiveness is derived from the resultant release of prostaglandins within the uterine compartment and hence its success is dependant on the responsiveness of the uterus and cervix. Patients' response to amniotomy alone is

often hard to predict and its effectiveness at inducing labour is poor (Keirse and van Oppen, 1990b). Its main value lies in sensitising the uterus to the action of oxytocin.

Amniotomy has a number of disadvantages. Once performed, the clinician is committed to delivery. This should not be delayed, as there is a risk of ascending infection. Fetal heart rate abnormalities occur more commonly in labour in patients with reduced liquor volume (Miyamura et al, 1997; Vergani et al 1996). There is also a risk of umbilical cord prolapse and trauma to mother, fetus or placenta, at the time of the procedure.

Stretching the cervix and sweeping the membranes is a traditional method of inducing labour. Controversy exists as to whether this is an effective form of induction of labour. Three studies, using weekly stripping of the membranes from 38 weeks, have shown that it results in earlier delivery and a reduction in pregnancy prolonged more than 41 weeks (McColgin et al, 1990; Berghalla et al, 1996; Wiriyasirivaj et al, 1996). These trials showed no higher incidence of adverse fetal or maternal outcome in those patients who had stripping of the membranes compared to those that had simply a cervical score assessment. However, Crane and co-workers (1997) showed no benefit of a single stretch and sweep over a cervical assessment, in inducing labour within the week, in a group of 150 primigravida at term.

Thus it can be seen, that although there are various drugs and induction methods in clinical use, none fit the ideal of being highly effective with the absence of side effects to mother and fetus. Consequently the search has continued for a drug that is able to mimic the natural physiology of labour onset and result in safe and expeditious delivery of the fetus. The recognition of the efficacy of misoprostol as an abortion agent has prompted the investigation of the drug's action on the uterus and cervix and its efficacy and safety as a cervical ripening and induction of labour agent in the third trimester.

1.3 MISOPROSTOL (CYTOTEC)

1.3.1 PHARMACOLOGY OF MISOPROSTOL.

Misoprostol is a methyl ester of PGE₁ with additional methylation at carbon 16 (Reynolds, 1996). This methylation results in reduced destruction of the prostaglandin in the lungs and kidneys and hence gives it a longer duration of action. This is a significant advantage over the other prostaglandins which are rapidly cleared by first pass metabolism.

Misoprostol is marketed for the treatment and prevention of peptic and duodenal ulcer disease (Reynolds, 1996). It is particularly effective in ulcers induced by non steroidal anti-inflammatory drugs. Misoprostol's mode of action is via both an antisecretory as well as a mucosal protective effect against various damaging substances (Wilson, 1987). The cellular and subcellular mechanism of action remains speculative (Doolley, 1991). The drug also has effects on other organ systems which have led to the investigation of other potential uses. Most notable amongst these has been its effect on the uterus (Lewis, 1985), immune system, cardiac conduction system, kidney and cartilage (Shield, 1992).

In large multicentre placebo controlled studies of the use of misoprostol in peptic ulcer disease it was found to cause menstrual complaints in 3.7% of women vs 1.7% who received placebo (Lewis, 1985). These complaints ranged from increased uterine contractility and dysmenorrhoea, to menorrhagia and intermenstrual bleeding. The effect of the drug on the pregnant uterus will be discussed further in sections 1.3.2 and 1.3.3 and is the subject of the presented studies in chapters 2 and 3 of this thesis.

In doses of less than 800 µg misoprostol is vasodilatory, natriuretic and diuretic while at higher doses it increases renal vascular tone and inhibits sodium and water excretion (Shield, 1992). Its use has been investigated in renal transplant patients where it has been shown to improve renal function and reduce the incidence of rejection (Reynolds, 1996).

Within cartilage, misoprostol alters the ground substance by stimulating glycosaminoglycan synthesis and is hence being investigated for its effect on rheumatological conditions (Shield, 1992).

Its described effect on the immune system may ameliorate inflammatory responses and autoimmune effects (Shield, 1992). It has been shown to inhibit histamine release in mucosal, skin and muscle cells (Shield, 1992) and modulate T-helper cell and monocyte function (Gold et al, 1994).

For use in peptic ulcer disease the drug is prescribed orally at a dose of 800 µg daily in 2 to 4 divided doses. With oral intake the drug is maximally absorbed in the stomach (Reynolds, 1996). Absorption is rapid and extensive metabolism occurs prior to, and during absorption. The active metabolite of misoprostol is the de-esterified derivative, misoprostol acid. The peak plasma concentration of the drug after oral absorption occurs approximately 30 minutes after ingestion and the elimination plasma half-life is 20 to 40 minutes (Reynolds, 1996). There is currently no published data on the pharmacokinetics of the tablet after vaginal insertion.

The most common side effects found with the drug are related to the gastrointestinal tract. Diarrhoea is found most frequently but other disturbances such as dyspepsia, flatulence, nausea and vomiting are also noted (Dooley, 1991).

Misoprostol is excreted in the breast milk and may lead to diarrhoea in the infant (Gibbon and Swanepoel, 1995). It is unknown to what degree misoprostol crosses the placenta and whether it has any effect of the fetus. The current understanding of its teratogenic potential will be discussed in section 1.3.2.

1.3.2 USE OF MISOPROSTOL IN FIRST AND SECOND TRIMESTER TERMINATIONS OF PREGNANCY.

Reports on the use of misoprostol for its oxytocic action first came from Brazil in the early 1990's (Schönhöffer, 1991; Costa and Vessey, 1993; Coêlho et al, 1993). In 1991, Schönhöffer described extensive use of misoprostol among women as an over-the-counter illegal abortifacient. Seventy three percent of women presenting at the University Hospital in Fortaleza with pregnancy related uterine bleeding in 1990 admitted to using the drug. He found that of 102 pharmacies consulted in the area, 83% of those who gave abortion advice, recommended the use of misoprostol. The recommended dosage regime varied, but 800 µg was the most commonly suggested. This was taken as 2 tablets orally and 2 tablets vaginally. Concern was however noted over its efficacy to induce complete abortion and its potential teratogenicity in pregnancies that continued.

The scientific appraisal of misoprostol as an abortifacient followed. Norman and co-workers (1991) studied the effect of misoprostol on the uterus in the first trimester when it was used both with and without the anti-progesterone mifepristone. They showed that misoprostol alone, increased uterine pressure in the ten week uterus but induced no regular uterine activity. This effect was qualitatively similar to that described with other prostaglandins. The effect appeared to be dose related with maximal effect occurring 30 minutes after the drug was administered. The authors reported minimal adverse side effects to the patient. The efficacy of misoprostol as a abortifacient however appeared lacking. It caused vaginal bleeding in 21 of 40 cases but resulted in complete abortion in only 2 of these cases.

Misoprostol's failure to cause complete abortions in the first trimester has been confirmed by other trials in which success rates are quoted at approximately 10% to 20% (Schönhöffer, 1991; Baird et al, 1992).

Pre treatment of patients with mifepristone prior to the use of misoprostol results in far higher complete abortion rates. Norman and colleagues showed a success rate of 86

% with 18 complete abortion in 21 cases (Norman et al, 1991). Concurrent use of anti-progestagens prior to exogenous prostaglandins has previously been shown to have a qualitative and quantitative change on uterine action resulting in an enhanced sensitivity to prostaglandins (Bygdeman and Van Look, 1988).

The role of misoprostol as a medical abortifacient has hence evolved with the adjuvant use of mifepristone. The combined use of these two drugs is highly effective and efficient at inducing abortion. Complete abortion rates have been shown to be between 85,7% and 97,5% (Norman et al, 1991; Baird et al, 1992; Peyron et al, 1993; Mckinley et al, 1993; El-Rafeay and Templeton, 1994). Side effects are minimal and patient acceptance high. Success rates are higher at lower gestational ages. Mckinley and co-workers (1993) showed a rate of 97,5% at less than 49 days gestation and a decrease to 89,1% at less than 63 days.

The combination of mifepristone and misoprostol has also been shown to be effective in the abortion of early anembryonic pregnancies and missed abortions (El-Rafeay et al, 1992)

Its efficacy to complete, incomplete or inevitable miscarriages is however contentious. Henshaw and co-workers (1993) found a 96% complete abortion rate when it was used in patients with incomplete or inevitable miscarriages. A similar study by de Jonge and co-workers (1995) failed to confirm this however. They found a success rate of only 13% compared to 97% found with surgical curettage.

Various dosage regimes for the use of the drugs have been evaluated. Mifepristone is usually given at a dose of 200 μg 48 hours prior to misoprostol. Misoprostol doses have ranged between 200 μg and 800 μg given either orally or per vaginam. Higher doses result in more gastrointestinal side effects and do not have any clinical benefits (El-Rafeay and Templeton, 1994). Giving the total dose of misoprostol in divided doses, appears effective, reduces side effects and results in lower total dosages being used in many patients (Peyron et al, 1993; El-Rafeay and Templeton, 1994).

When used with Mifepristone, oral use of misoprostol is less effective at procuring a complete abortion than equivalent vaginal doses. El-Refaely and co-workers (1995) found a 95% success rate with vaginal insertion versus 85% with oral misoprostol ($P=0.03$). Side effects were also more common with the oral route.

As mifepristone is not widely available, methotrexate has also been evaluated as an adjuvant therapy for use with misoprostol to improve complete abortion rates. Used at a dose of 50mg per square metre of body surface area, 5 to 7 days before 800 μg misoprostol, it resulted in abortion rates of up to 97% (Creinin and Vittinghof, 1994; Hausknecht, 1995; Schaff et al, 1995). Side effects of nausea, diarrhoea and vomiting were noted, but 93% of patients felt the procedure was acceptable (Schaff et al, 1995).

An increasing body of literature exists describing the use of misoprostol as a cervical priming agent prior to surgical dilatation and curettage in first trimester abortion. Misoprostol significantly improves cervical dilatation (both subjectively as well as measured by Bishop's score) when compared to placebo and to intravaginal gemeprost (El-Refaely et al, 1994; Bughalo et al, 1994a; Ngai et al, 1995). Side effects are minimal and blood loss similar.

Few studies have looked particularly at the use of misoprostol in the second trimester. A prospective randomised trial by Jain and co-workers (1994) compared 200 μg misoprostol 12hrly to 2 mg PGE_2 3hrly in 55 patients in the second trimester. These patients had either an intrauterine fetal demise or required termination of pregnancy for medical or genetic reasons. Abortion was induced in 89% of patients with misoprostol and 81% with PGE_2 . Forty three percent of the patients who received misoprostol had complete abortions and 32% who received PGE_2 . These success rates were not significantly different and the induction of labour to delivery intervals were similar. Side effects of pyrexia, diarrhoea and vomiting were more common in those who received PGE_2 . In a descriptive trial of 132 women in the second trimester by Bughalo and co-workers (1993), 88.6% had successful non surgical expulsion of the fetus within 56 hours. Doses between 800 μg and 1600 μg of misoprostol were used. El-Refaely and Templeton (1995) compared two misoprostol dosage regimes after pre

treatment with mifepristone and found a successful abortion rate of 97% in the second trimester. Bughalo and co-workers (1994) evaluated efficacy in 72 patients with an intrauterine fetal death between 18 and 40 weeks. They used 100 µg misoprostol 12 hourly for 48 hours by which time all patients had delivered. The mean IOL to delivery interval was 12.6 hours.

Concern over the use of misoprostol in the first and second trimester has been expressed because of potential teratogenicity should the pregnancy continue. Five cases of skull and scalp malformations, consisting of well circumscribed defects of the cranium and overlying scalp (exposing the dura mater) have been described in women who used misoprostol in the first trimester to terminate pregnancy (Fonseca et al, 1991). Three of these women claimed that this was the only drug used in the first trimester.

Seven cases of limb deficiency with or without Möbius sequence have also been reported from Brazil in patients who tried unsuccessfully to abort their fetuses in the first trimester with misoprostol (Gonzalez et al, 1993). No other common or explanatory factors for these abnormalities could be found other than the association with the use of misoprostol. How the drug may cause these defects is uncertain (Gonzalez et al, 1993; Shepard, 1995).

A report by a nation wide Teratogenic Information System in Brazil however notes that no major malformations were detected in 17 prospectively studied live births from a group of 29 pregnant women who had taken various doses of misoprostol as an abortifacient in the first trimester (Schuler, 1992). Searle, the marketers of misoprostol have shown no evidence of misoprostol as a teratogen in its animal toxicology program with doses as high as 625 times the human dose (Downie, 1991). The company does not support the use of misoprostol in pregnancy however mainly because of its oxytocic properties. The teratogenic potential of the drug remains uncertain.

1.3.3 USE OF MISOPROSTOL IN THE TERM PREGNANCY.

At the time of embarking on the current trial, few randomised studies had been conducted on the use of misoprostol in term pregnancies. It had been compared to placebo, oxytocin and prostaglandins (dinoprostone and prepidil gel) in cervical ripening and induction of labour (IOL) (Fletcher et al, 1993; Sanchez-Ramos et al, 1993; Fletcher et al, 1994; Wing et al 1995a; Wing et al 1995b; Bughalo et al ,1995). These trials used various dosage regimes and routes of administration of the drug and had involved only small numbers of patients. Their results suggested that misoprostol may be a successful induction of labour agent in the term pregnancy but raised concerns over possible side effects to the mother and fetus associated with use of the drug. A tabulated summary of the published trials on the use of misoprostol is found on page 57, Table 3.5.

Fletcher and co-workers (1993) published a randomised double blind placebo controlled trial on the use of misoprostol as a cervical ripening agent in the term pregnancy. Forty five women were randomised to receive either 100 µg of crushed misoprostol in a hydroxy-ethyl gel intravaginally or placebo prepared and inserted in a similar fashion. This trial showed a significant improvement in Bishop's score over 12 hours as well as a significant reduction in the overall induction of labour (IOL) to delivery interval with misoprostol. No adverse outcome to mother or fetus was noted with the drug.

Further trials compared the drug to oxytocin and to Prostaglandin E₂ (PGE₂) gel. Sanchez-Ramos and co-workers (1993) randomised 129 patients to receive either 50 µg misoprostol (half of a 100 µg tablet) intravaginally 4 hourly until active labour was achieved or an oxytocin infusion preceded by PGE₂ gel if the cervix was unfavourable. Prostaglandin gel was used as a cervical ripening agent in 45% of those patient randomised to the oxytocin arm. They found that an average of 1.4 doses of 50µgs of misoprostol resulted in a significant reduction in the IOL to delivery interval

over oxytocin. In those patients who had received misoprostol, only 22% required augmentation with oxytocin. There was however, a significant increase in the incidence of tachysystole in the misoprostol arm. This did not appear to have any adverse effect on mother or fetus and the caesarean section rate was unchanged. The authors suggested that the drug was not only a cervical ripening agent but also an oxytocic.

Bugalho and co-workers (1995) similarly compared misoprostol and oxytocin and showed misoprostol resulted in a significantly reduced IOL to delivery interval, especially in patients who had a Bishop's score of < 6 at recruitment.

Fletcher and co-workers (1994) compared 100 µg misoprostol to 3 mg dinoprostone as a cervical ripening and IOL agent. In 63 patients, they showed a significant improvement in the change in Bishop's score over 24 hours but were unable to show any significant improvement in the IOL to delivery interval or the achievement of a vaginal delivery. No difference was found in either maternal or fetal complications. Fetal heart rate (FHR) monitoring was however achieved with auscultation alone in the most cases.

Further studies have been published comparing misoprostol to intracervical prepidil gel. Wing and co-workers (1995) randomised 130 patients to receive either misoprostol 50 µg 3 hourly (to a maximum dose of 300 µg) or prepidil gel 0.5 mg 6 hourly (to a maximum dose of 1.5 mg). With an average dose requirement of 2.4 ± 1.3 doses of misoprostol there was significant reduction in the IOL to delivery interval and need for oxytocin augmentation. Tachysystole was significantly more common in the misoprostol group. Although the passage of meconium by the fetus occurred more commonly in the misoprostol group, there was no difference in the presence of abnormal fetal heart rate patterns, caesarean section rate for fetal distress, Apgar scores at birth or admission to the Neonatal Intensive Care Unit (NICU).

Due to the high frequency of tachysystole and of meconium staining of the liquor with the 50 µg regime a further study was done using a lower dose of 25 µg misoprostol 3

hourly to a maximum dose of 200 µg (Wing et al 1995b). One hundred and seventy five patients were recruited. The average number of doses required for delivery was 2.6 ± 1.9 doses. With a lower number of doses the IOL to delivery interval was still significantly less than with prepidil gel. The incidence of tachysystole was reduced by 50 % using the lower dose regime but was still higher than that found with prepidil gel. There was however no change in the rate of abnormal FHR patterns with the lower doses and the incidence of meconium staining of the liquor remained the same.

Subsequent to embarking on this trial, further studies have been published showing similar findings; an improvement in the cervical scores and reduction in IOL to delivery interval with misoprostol. (Howarth et al, 1995; Varaklis et al, 1995; Chuck and Huffaker, 1995; Magtibay, 1995; Mundle and Young, 1996). These trials all compared the drug to prepidil gel in various regimes and dosages. No adverse effects were noted to mother or fetus. All these studies however compared only small numbers of patients, the largest involving 138 patients.

Misoprostol hence offers a potentially more effective and efficient cervical ripening and IOL agent in the term pregnancy. The literature to date suggests superiority to the conventionally used agents of oxytocin, dinoprostone and prepidil gel. Use of misoprostol also offers a significant cost saving. The current retail price of misoprostol at R1 62 per 200 µg tablet compared to R87 00 for 1 mg prostaglandin E₂ gel. From the small studies already performed the drug appeared not to have any adverse outcomes on the mother or fetus.

As all the published studies were relatively small and the potential advantages of this drug clinically and economically very significant, the following two studies were embarked upon.

The aim of the studies were to compare the efficacy and safety of misoprostol and prandin gel as agents for cervical ripening and induction of labour in the term pregnancy. The agents' ability to ripen the cervix and to induce labour, were addressed

separately with two studies that were run concurrently. The aims, materials and methods, results and discussion of the two trials are presented below in chapters 2 and 3. These are then followed by general conclusions, in chapter 4, on the role of misoprostol in initiation of labour at term.

CHAPTER 2

A RANDOMISED TRIAL TO COMPARE THE EFFICACY AND SAFETY OF MISOPROSTOL WITH PRANDIN GEL IN CERVICAL RIPENING AT TERM.

2.1 AIM OF STUDY

To compare the efficacy and safety of misoprostol with prandin gel as an agent for cervical ripening at term. The specific objective was to compare the ability of the two drugs to bring about a significant change in Bishop's score of the cervix over a twenty four hour period.

2.2 MATERIAL AND METHODS.

The study was a centrally-randomised, controlled study conducted in the three hospitals of the Peninsula Maternal and Neonatal Service (PMNS). These hospitals were Groote Schuur Hospital, Somerset Hospital and Mowbray Maternity Hospital. Ethical approval was obtained from the University of Cape Town Research and Ethics Committee.

The trial started on 1 June 1995. Patients were recruited if they required cervical ripening prior to induction of labour, but delivery was not considered imperative within 24 hours. Patients eligible for recruitment were those with a singleton fetus of more than 37 weeks gestation in whom membranes were unruptured, cardiotocographic monitoring showed no evidence of fetal distress and there were no progressive or painful uterine contractions. Patients were excluded from the trial if they had had a previous caesarean section or other uterine surgery or if there was any known contraindication to prostaglandin ripening. Written informed consent was obtained from all patients prior to recruitment to the trial.

Randomisation was performed by the attending clinician selecting a sealed opaque envelope containing written instructions concerning the drug to be given. Two hundred and forty envelopes, half containing cards for misoprostol and half for prandin gel, were made up at the start of the trial, randomly shuffled and then distributed to the three participating hospitals.

The cervical Bishop's score was established prior to insertion of the drug (Bishop, 1964). A cardiotocograph tracing was obtained for at least 10 minutes prior to the onset of the trial to exclude any evidence of fetal distress. It was then run continuously for at least 4 hours after administration of the drug. Patients were randomised to receive either misoprostol, 100 µg (half a 200 µg tablet) or prandin gel, 1 mg, in the posterior vaginal fornix.

If labour was initiated by the drug, it was managed according to standard labour ward protocols. Oxytocin augmentation was used if cervical dilation was less than 4 cm in 4 hours and there were less than 3 contractions of 40 second duration in 10 minutes. A standard infusion regime of 2mu/min, increasing half hourly to a maximum of 8mu/min, or until adequate contractions were achieved, was used. This was only initiated if there were no signs of cephalopelvic disproportion. Analgesia was used at request of the patient. Opiate analgesia was available at all units but only two of the hospitals offered epidural analgesia. Cardiotocography was performed throughout labour.

If labour was not initiated by the trial drug and either the maternal or fetal condition deteriorated, delivery was expedited by either amniotomy with oxytocin infusion or caesarean section, whichever was appropriate. The patients who did not go into labour and remained undelivered 24 hours after insertion of the drug, had a repeat vaginal assessment by the same clinician and a second Bishop's score recorded.

The demographic characteristics of maternal age, gravidity, parity, gestational age and indication for induction of labour were recorded in all cases. Any maternal side effects such as nausea, vomiting, diarrhoea or fever greater than 37.5°C were noted. If labour ensued, then delivery details including, mode of delivery, drug administration to

delivery interval, analgesic usage, oxytocin requirements and complications of the third stage of labour were recorded. Post partum haemorrhage was defined as an estimated blood loss of greater than 500mls.

Uterine activity patterns were recorded by the attending clinician. Tachysystole was defined as 5 or more contractions per 10 minutes in two consecutive 10 minute periods. Hyperstimulation was defined as contractions lasting more than 2 minutes or the presence of coupled contractions.

The presence of meconium staining of the liquor at birth was noted. Neonatal Apgar scores were assigned by the attending paediatrician or paediatric nurse at 1 and 5 minutes after birth. All admissions to the Neonatal Intensive Care Unit (NICU) were documented.

2.3 STATISTICS

The null hypothesis formulated was that the number of patients converted from an unfavourable Bishop's score of less than or equal to 4, to one greater than 4, was no different if either misoprostol or prandin gel was used as a cervical ripening agent.

The number of patients recruited to the study was calculated based on alpha set at 0.05 and a beta at 80%. Initial calculations showed 120 patients needed to be recruited in each arm of the trial. Randomisation was based on this figure. However review of the statistics based on the results of the meta-analysis in the Cochrane Data Base showed that the recruitment of 72 patients in each group would be sufficient to show the required improvement (Keirse, 1994a). This was based on the ability of PGE₂ gel to secure a good improvement in Bishop's score in 72% of patients when compared to placebo. It was therefore postulated that a further 30% improvement in number of patients achieving a ripe cervix would be clinically relevant and the sample size calculation was based on this. The 240 patients originally ascribed necessary were recruited to the trial and statistical analysis performed on these.

The Student's *t* test was used to analyse the continuous data of maternal age, gestational age, birth weight and IOL to delivery interval. The Chi squared test was used to analyse the categorical data of nuliparity, indication for induction of labour, achievement of delivery within 24 hours, number of patients with favourable and unfavourable Bishop's scores, mode of delivery, maternal complications and requirements for oxytocin and analgesia. Mann-Whitney *u* test was used to analyse differences in neonatal Apgar scores.

1.4 RESULTS

Two hundred and forty patients were recruited to the trial. One hundred and twenty received misoprostol and 120 received prandin gel.

Data was analysed on 113 patients in the misoprostol group and 116 patients in the prandin gel group. The reasons why patients were not included in the final analysis is tabulated below in Table 2.1.

Table 2.1. Number of patients excluded from final analysis and reasons for their exclusion.

	<u>MISOPROSTOL</u>	<u>PRANDIN GEL</u>
Delivery data untraceable	5	3
Incorrect randomisation *	2	0
Absconded	0	1

* Two patients in the misoprostol arm were incorrectly randomised and did not receive the drug - one was less than 37 weeks gestation and 1 patient was found to have a Bishop's score of 11 after randomisation and did not require a cervical ripening agent.

Two patients in the misoprostol arm had their tablets removed within the first four hours after insertion because of the development of tachysystole and went on to have induction of labour by other methods. The decision to remove the tablets was made by the patients attending clinicians and was not part of the study protocol. These patients were analysed in the misoprostol group.

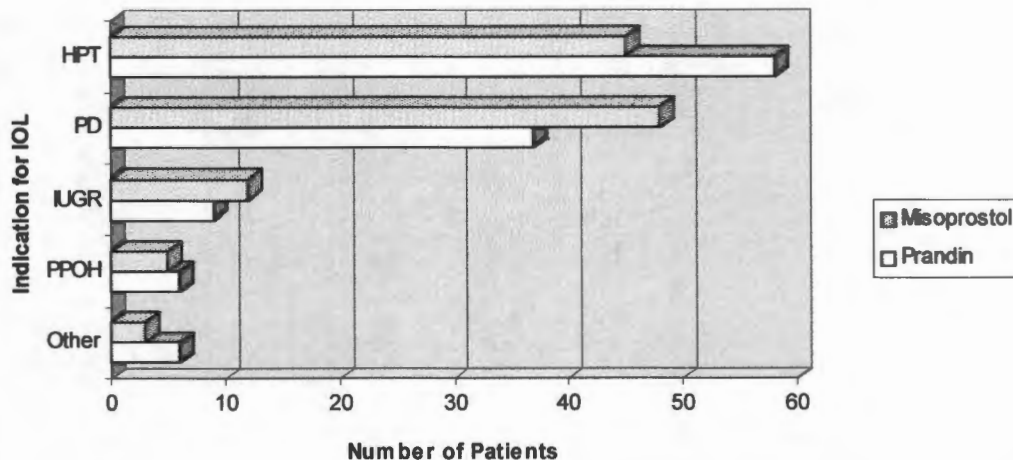
There were no differences in the demographic characteristics of maternal age, nulliparity, gestational age and birth weight in the misoprostol and prandin groups. There were 65 patients in each group with a Bishop's score of 4 or less at the onset of the trial. (Table 2.2) The range of Bishop's scores were from 0 to 8 with both drugs.

Table 2.2. Demographic characteristics of the trial patients.

	<u>MISOPROSTOL</u> <i>n</i> = 113	<u>PRANDIN GEL</u> <i>n</i> = 116	Significance
Maternal Age (years)	26.6 (6.4)	25.5 (5.4)	NS
Nulliparous (n)	46 (40.7%)	62 (53.4%)	NS
Gestational Age (weeks)	40.1 (2.3)	39.8 (2)	NS
Birth Weight (grams)	3150 (456)	3192 (582)	NS
Bishop's score \leq 4 at onset of trial (n)	65 (57.5%)	65 (56%)	NS

Data is expressed as mean (standard deviation) or number (percentage)

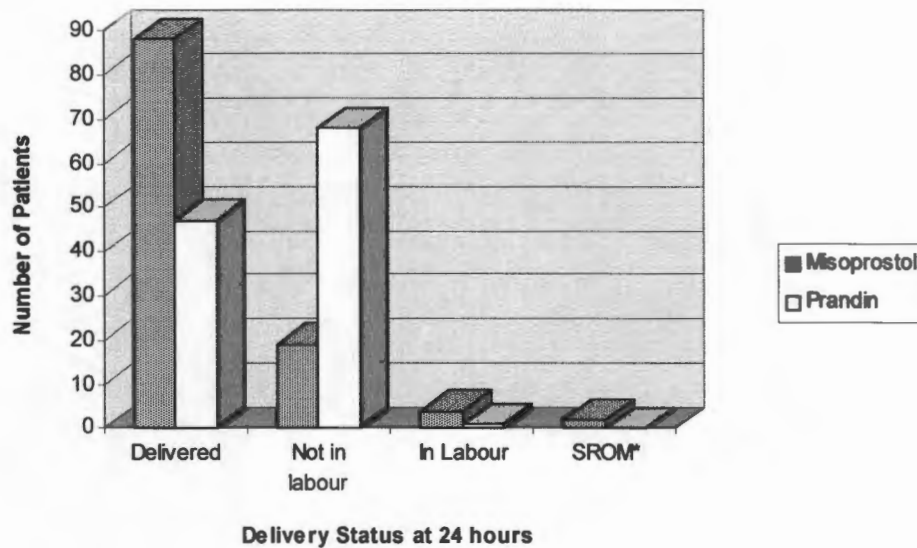
There were no significant differences between the two groups in the indications for cervical ripening. (Graph 2.1) The most common indication was hypertensive disease, followed by post dates and intrauterine growth restriction (IUGR).



HPT - All hypertensive disease - including, pre-eclampsia and chronic hypertension, PD - Post dates, IUGR - Intrauterine growth restriction, PPOH - Poor past obstetric history, Other - included Diabetes, Rhesus disease, previous antepartum haemorrhage, hyperemesis gravidarum and mild hydrocephalus.

Graph 2.1. Indications for induction of labour (IOL).

The delivery status at 24 hours after the insertion of the drug is shown below in Graph 2.2. Eighty eight patients (77.8%) randomised to the misoprostol arm, delivered within 24 hours of receiving the drug; a further 4 were in labour and 2 had ruptured membranes at the time of the 24 hour reassessment. Nineteen patients had a repeat Bishop's score after 24 hours. In the prandin group 47 (40.5%) patients delivered within 24 hours and 1 was in labour at the 24 hour assessment time. Sixty eight patients had a repeat Bishop's score after 24 hours. The number of patients delivered within 24 hours was significantly different between the two drugs. ($P < 0.001$ OR 5.7 CI 2.79 to 9.63)



*SROM - Spontaneous Rupture of Membranes

Graph 2.2. Delivery and labour status of patients at 24 hours after receiving the cervical ripening agent.

Of those patients that delivered within 24 hours, eighty patients (89.9%) who received misoprostol and 38 (80.9%) who received prandin gel went into labour on a single dose of the drug. In those patients in whom labour was not initiated, delivery was expedited in 5 patients in the misoprostol group for maternal indications (4 for deteriorating gestational proteinuric hypertension (GPH) and 1 for an unexplained antepartum haemorrhage) and 3 for fetal distress. In the prandin group, 7 were delivered for maternal indications (all 7 for deteriorating GPH) and 2 were delivered for fetal distress.

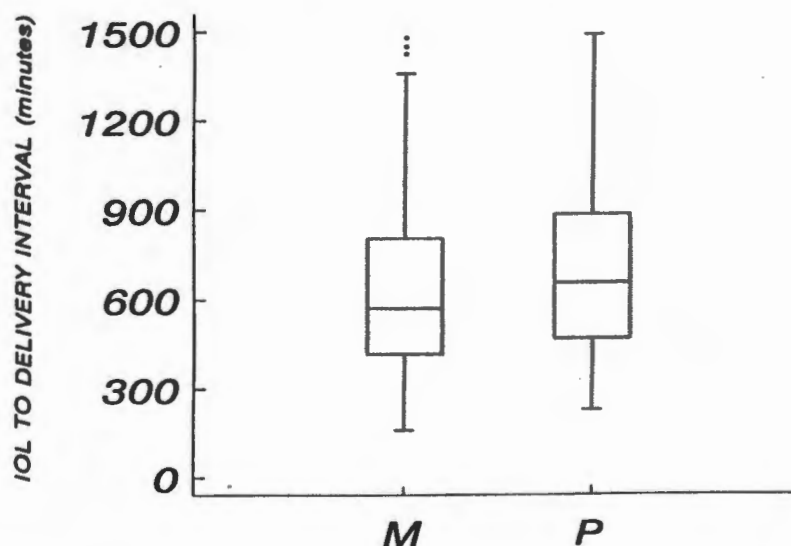
In those patients who did not deliver within 24 hours, both drugs showed a significant improvement in the number of patients converting from an unfavourable Bishop's score (score ≤ 4) to a more favourable one (score > 4). Neither drug however showed superiority over the other. Misoprostol converted a further 9 patients (36%) from an unfavourable to a more favourable score and prandin gel, a further 21 patients (30.4%). (Table 2.3)

Table 2.3. Table showing the number of patients with favourable Bishop's scores pre cervical ripening and after 24 hours, in those patients undelivered at 24 hours.

	<u>MISOPROSTOL</u> <i>n</i> = 25	<u>PRANDIN GEL</u> <i>n</i> = 69
Patients with Bishops score > 4 pre ripening	9 (47.3%)	25 (36.2%)
Patients with Bishops score > 4 after 24 hours	18 (72%)	46 (66.7%)

Data is expressed as number (percentage)

The overall mean induction of labour to delivery interval in those that delivered in less than 24 hours was 9 hours 23 minutes (SD = 7h36) for misoprostol and 10 hours 31 minutes (SD = 5h07) for prandin gel. This difference was not statistically significant. See Graph 2.3 below for graphical representation. The duration of labour in those patients who achieved a vaginal delivery within twenty four hours was also no different between the misoprostol and prandin groups. This was 9 hours 22 minutes (SD = 5h36) with misoprostol and 10 hours 45 minutes (SD = 4.41)with Prandin gel.



Graph 2.3. Box and whisker plot showing the distribution of cervical ripening to delivery intervals, in minutes, in those patients who delivered in less than 24 hours.

In those patients delivered within 24 hours of receiving the drug, the caesarean section rate was similar at 13.6% with misoprostol and 12.7% with prandin gel. The mode of delivery and indications for caesarean section are found in Table 2.4. The major indication for caesarean section was fetal distress in both groups with 9 (10.2%) patients requiring a caesarean section for fetal distress in the misoprostol group and 3 (6.4%) in the prandin group.

Table 2.4. Mode of delivery and indication for caesarean section in those patients who delivered within the 24 hour ripening period.

	<u>MISOPROSTOL</u> <i>n</i> = 88	<u>PRANDIN GEL</u> <i>n</i> = 47	Significance
Normal Vertex Delivery	74 (84.1%)	40 (85.1%)	NS
Instrumental Delivery	2 (2.2%)	1 (2.1%)	NS
Caesarean Section	12 (13.6%)	6 (12.7%)	NS
Indication:			
- Fetal Distress	9	3	NS
- Failure to progress	1	1	NS
- GPH *	1	1	NS
- Failed vacuum extraction	1	1	NS

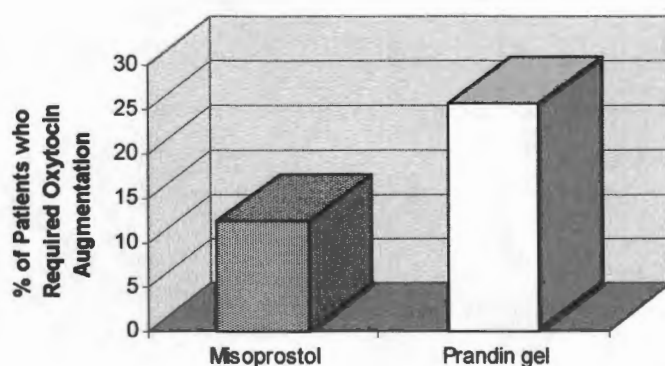
Data expressed as number (percentage)

* GPH -Gestational proteinuric hypertension

Umbilical cord pH's were not measured on all the patients who had a caesarean section for fetal distress. In the misoprostol group, 5 of the 9 patients had a cord pH measured post delivery and in 2 of these the pH was less than 7.2. In the prandin Group, 2 of the 3 patients had a cord pH measured and 1 had a pH less than 7.2. No specific indication for induction of labour resulted in a higher chance of caesarean section for fetal

distress and there was no higher incidence of caesarean section for fetal distress in those patients who experienced tachysystole or who received oxytocin.

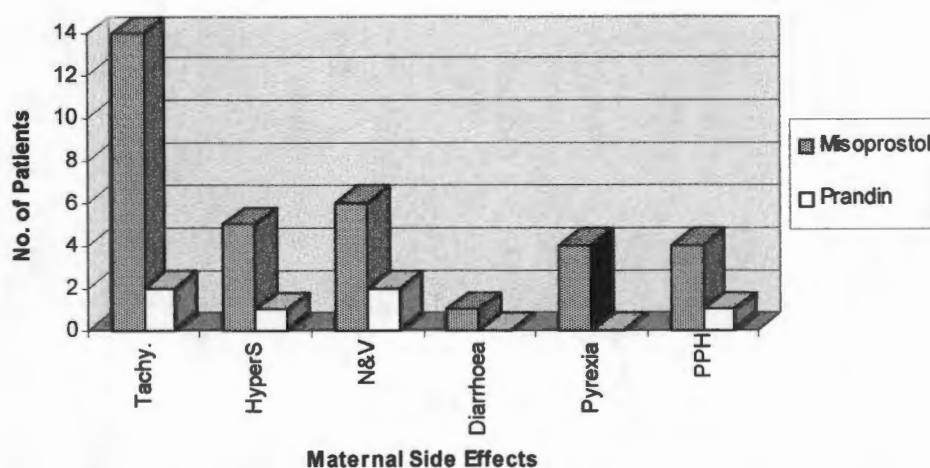
In those patients who delivered within 24 hours of recruitment, significantly more patients in the prandin group required oxytocin augmentation for delay in the first stage of labour (11(12.5%) patients in the misoprostol group and 12 (25.5%) patients in the prandin group). ($P < 0.05$ OR = 0,42 CI 0,15 to 1.13) (Graph 2.4)



Graph 2.4. Graph showing percentage of patients who required oxytocin augmentation, in those patients who delivered within 24 hours of receiving the ripening agent.

Maternal side effects were uncommon and are shown below in Graph 2.5. Nausea, vomiting and diarrhoea were no more common with either drug. A pyrexia of more than $37,5^{\circ}$ C was noted in 4 patients who received misoprostol but in none who received prandin gel. In three of these patients this was related to the presence of clinical infection. Post partum haemorrhage estimated at > 500 mls occurred in 4 patients who received misoprostol and 4 patient who received prandin gel. Two patients who received misoprostol developed abruptio placentae during the course of the labour. One was delivered by caesarean section for fetal distress, and in the second, the abuptio placentae was noted following vaginal delivery. Both patients had received cervical ripening for mild GPH.

Tachysystole occurred significantly more commonly with misoprostol than prandin gel. Fourteen patients (12.4%) who received misoprostol and 2 patients (1.7%) who received prandin gel experienced this increased frequency of contractions. ($P < 0.01$) Hyperstimulation occurred seldom with the two drugs. It occurred in 5 patients (4.4%) who received misoprostol and 1 patient (0.8%) who received prandin gel.



Tachy. - Tachysystole, HyperS. - Hyperstimulation, N&V- Nausea and vomiting, PPH - Post partum haemorrhage.

Graph 2.5 Maternal side effects experienced with the cervical ripening agents.

Analgesic requirements in those patients who received misoprostol were not significantly different from those that received prandin gel. In the misoprostol group, 5 patients had epidural analgesia and 51 patients opiate analgesia, a total of 47.8% requesting analgesia altogether. In the prandin group 54 had opiate analgesia and 2 received epidural analgesia. Thus a total of 48.2% requested analgesia in the prandin arm.

There was no difference between the two groups with regard to fetal complications (assessed by meconium staining of the liquor, Apgar score < 7 at 5 minutes after birth or admission to NICU). (Table 2.5) There were no intrapartum or neonatal deaths in the trial. Two neonates were admitted to the NICU with the diagnosis of asphyxia neonatorum. Both of these mothers had received misoprostol as a ripening agent. In one patient an abruptio placentae developed during the course of labour with resultant

fetal distress and the second was delivered rapidly per vaginam following a cord prolapse at full dilation.

Table 2.5. Neonatal outcome in those patients delivered within 24 hours of cervical ripening.

	<u>MISOPROSTOL</u> <i>n</i> = 88	<u>PRANDIN GEL</u> <i>n</i> = 47	Significance
Meconium Staining of Liquor	1 (1.1%)	1 (2.1%)	NS
Apgar score <7 at 5 minutes	2 (2.3%)	0	NS
Admission to the NICU	2 (2.2%)	0	NS

Data is expressed as number (percentage)

2.5 DISCUSSION

The cervix that is firm, long and closed creates a significant barrier to the induction of labour. It is well known that cervical ripening prior to induction of labour by amniotomy and/or oxytocin infusion, results in a shortened induction to delivery interval as well as a reduction in caesarean section rate for failed induction of labour (Keirse, 1994). Shortened labours and lower failure rates are associated with less oxytocin usage, analgesic requirements and febrile morbidity (Keirse and van Oppen, 1990a).

This trial has evaluated the efficacy and safety of misoprostol as a cervical ripening agent and compared it to intravaginal PGE₂, in the form of prandin gel. It has shown that misoprostol is able to cause cervical ripening and effectively induce labour and delivery in the term pregnancy. The results show that misoprostol is more than twice as

effective as prandin gel in initiating labour and leading to delivery within 24 hours of the onset of cervical ripening.

It is evident from the study that misoprostol does not act by ripening the cervix alone, but also has oxytocic properties. This is a characteristic also found with other clinically used Prostaglandins (Keirse and van Oppen, 1990a). The significantly reduced oxytocin requirements associated with misoprostol administration also reflects the oxytocic efficacy of the drug. In 12% of patients misoprostol resulted in an abnormally high frequency of contractions. Further research is required to establish the contribution of contraction frequency, on the efficacy of misoprostol-induced labours.

Because of this oxytocic effect, misoprostol cannot be recommended in patients in whom only cervical ripening is required and immediate delivery is not intended. It is suggested that in these cases the drug should be used in conjunction with a tocolytic as has been used with PGE₂ (Insull et al, 1989; Taylor et al, 1990).

The high rates of successful induction of labour found with misoprostol are consistent with the reported literature. In randomised trials comparing a single 100µg dose of misoprostol to placebo and to dinoprostone, misoprostol has shown induction of labour rates between 58% to 96% (Fletcher et al, 1993; Fletcher et al, 1994; Srisomboon et al, 1996). The delivery rate of 40.5% found with prandin gel in this trial is similar to the 36,4% recorded by Keirse in a meta-analysis from the literature over the last 20 years (Keirse, 1994a).

Misoprostol and prandin gel were shown to have similar efficacy in promoting cervical ripening in those patients in whom labour was not initiated within 24 hours. They both converted a further 30% of patients to a Bishop's score of greater than 4 during this period. This clinical improvement in cervical ripeness has been shown to facilitate a more successful induction of labour (Keirse and Van Oppen, 1990a). These findings are consistent with those in the literature where misoprostol has been shown to promote cervical ripening. Mean Bishop's score changes of between 5.3 and 8 points have been reported with its use (Fletcher et al, 1993; Fletcher et al, 1994). Misoprostol

has also been associated with a mean change in cervical length of 24mm over 12 hours (Srisomboon et al, 1996).

The significantly higher incidence of tachysystole induced by misoprostol is a consistent finding throughout the reported literature (Fletcher et al, 1993; Fletcher et al, 1994; Srisomboon et al, 1996). Increasing the frequency of contractions may facilitate induction of labour but its effects on the mother and fetus are still uncertain (Curtis et al, 1987). It is known that a period of 2.3 minutes between contractions is needed to allow adequate blood flow to the placenta and oxygenation of the fetus (Peebles et al, 1994). More frequent contractions lead to progressive fetal hypoxia. This may be critical to a fetus that is already stressed. This trial was unable to show any association with tachysystole and adverse outcome to the fetus. However the sample size was too small to exclude this possibility. No specific adverse maternal complications arose because of tachysystole in the misoprostol patients and it did not increase analgesic usage.

Other maternal side effects appeared to be uncommon when misoprostol is used at these doses.

Removal of the tablet in two patients who developed tachysystole and associated late fetal heart rate decelerations, resulted in the fetal heart trace returning to normal. Tablet retrieval was easy and both patients had induction of labour with other means. Tablet removal in such situations should be recommended as part of fetal resuscitation measures while decisions are made regarding the route of delivery.

Consequently, from this trial, it appears that misoprostol induces labour and results in delivery in over three quarters of the patients in whom it is used as a cervical ripening agent. In those patients in whom labour is not induced, it significantly increases the number of patients with a more favourable cervical score.

CHAPTER 3

RANDOMISED TRIAL COMPARING MISOPROSTOL WITH PRANDIN GEL IN INDUCTION OF LABOUR AT TERM.

3.1 AIM OF STUDY

To compare the efficacy and safety of misoprostol with prandin gel as agents used for induction of labour (IOL) at term. The specific objective is to compare the two drugs' ability to secure vaginal delivery within 12 hours of drug insertion.

3.2 MATERIALS AND METHODS

As with the cervical ripening arm, this study was a centrally randomised trial conducted in the three hospitals of the Peninsula Maternal and Neonatal Service (PMNS). Prior to embarking on the trial ethical approval was obtained from the University of Cape Town Research and Ethics Committee.

Patients were recruited to the induction of labour arm of the trial if they required IOL for either maternal or fetal reasons and delivery was felt to be necessary within 24 hours. Inclusion and exclusion criteria were otherwise the same as for the cervical ripening arm of the trial.

Randomisation was again performed by the clinician selecting a sealed opaque envelope containing instructions concerning the drug to be given. Three hundred and forty envelopes, half containing instructions to use misoprostol and half to use prandin gel were made up centrally at the start of the trial, randomly shuffled and then distributed to the three participating hospitals.

Patients were randomised to receive either misoprostol, 100 µg (half a 200 µg tablet) or prandin gel, 1 mg, in the posterior fornix. A Bishop's score of the cervix was established prior to insertion of the drug. A fetal heart rate tracing was obtained for at least 10 minutes prior to the onset of the trial to exclude any evidence of fetal distress and was run continuously thereafter for the duration of the labour in the majority of patients.

If labour was not established after 4 hours and the cervix remained too unfavourable to allow amniotomy, then a further dose of the drug was inserted. In the absence of signs of cephalo-pelvic disproportion (CPD), oxytocin augmentation was started if cervical dilation was less than 4 cm in 4 hours and there were less than 3 contractions of 40 second duration in 10 minutes. A standard infusion regime was used of 2mu/min. This was increased half hourly until adequate contractions were achieved or to a maximum of 8mu/min. Induction was said to have failed if, 4 hours after the second dose of the drug there were no progressive uterine contractions and the cervix remained unfavourable for amniotomy. Analgesia was used at patient request. Opiate analgesia was available at all units but only two of the units offered epidural analgesia.

The cardiotocograph tracings were analysed post delivery by an independent observer. Uterine tachysystole was defined as the presence of more than 5 contractions in 2 consecutive 10 minute periods and hyperstimulation as either contractions lasting longer than 2 minutes or the presence of coupled contractions. The tracings were analysed for the hour immediately after the drug was inserted, for an hour period every 4 hours thereafter and finally the last hour pre delivery.

Demographic data of age, gravidity, parity, gestational age at induction and indication for IOL was recorded for all patients. Delivery occurring within 12hours, mode of delivery, induction of labour to delivery interval, analgesic and oxytocin requirements, third stage complications, maternal side effects and fetal outcome were all noted.

3.3 STATISTICS

The null hypothesis formulated was that misoprostol was as effective as prandin gel in initiating labour and leading to delivery within 12 hours in the term pregnancy.

Three hundred and forty patients were recruited to the study. This was calculated with an alpha set at 0.05 and a beta at 80%. It was based on a failed delivery rate of 47 % with PGE₂ when compared to placebo as found by a meta analysis in the Cochrane Data Base (Keirse, 1994b). It was postulated that a 40% reduction in this failure rate after 12 hours would be clinically significant.

Appropriate statistical analysis was performed on the data with the Student t test used to analyse continuous data and the Chi squared test used to analyse categorical data. Mann-Whitney u test was used to analyse differences in Apgar and Bishop's scores.

3.4 RESULTS

According to the sample size calculation, 340 patients were recruited to the trial. One hundred and seventy received misoprostol and 170 received prandin gel.

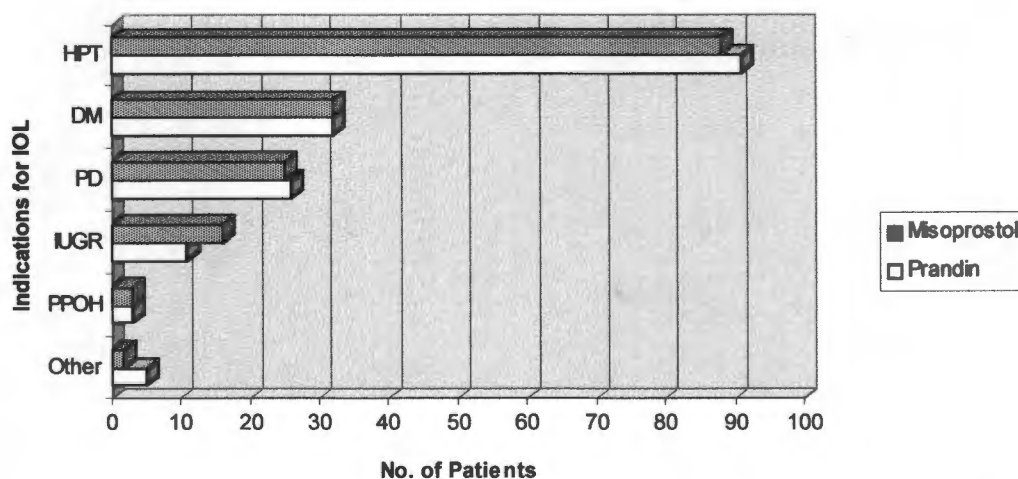
The distributions of maternal age, parity, gestational age and birth weight were similar in the two groups. (Table 3.1) Eighty one (47.9%) patients who received misoprostol and 87 (51.4%) who received prandin gel had a Bishop's score of ≤ 4 at the onset of the trial. (Table 3.1) The range of Bishop's scores was 0 to 9 in the misoprostol group and 0 to 8 in the prandin group.

The indications for induction of labour were similar in the two groups. (Graph 3.1) The most common indication was hypertensive disease, followed by diabetes and post dates.

Table 3.1 Demographic data of the trial patients

	<u>MISOPROSTOL</u> <i>n</i> = 170	<u>PRANDIN GEL</u> <i>n</i> = 170	Significance
Maternal age (weeks)	26.9 (6)	27.3 (6.3)	NS
nulliparous (n)	74 (43.5%)	77 (45.3%)	NS
Gestational Age (weeks)	38.8 (1.3)	38.8(1.5)	NS
Birth Weight (grams)	3087 (540)	3028 (544)	NS
Bishops Score ≤ 4 at onset Trial (n)	81 (48.2%)	87 (47%)	NS

Data is expressed as number (percentage) or as mean (Standard Deviation)

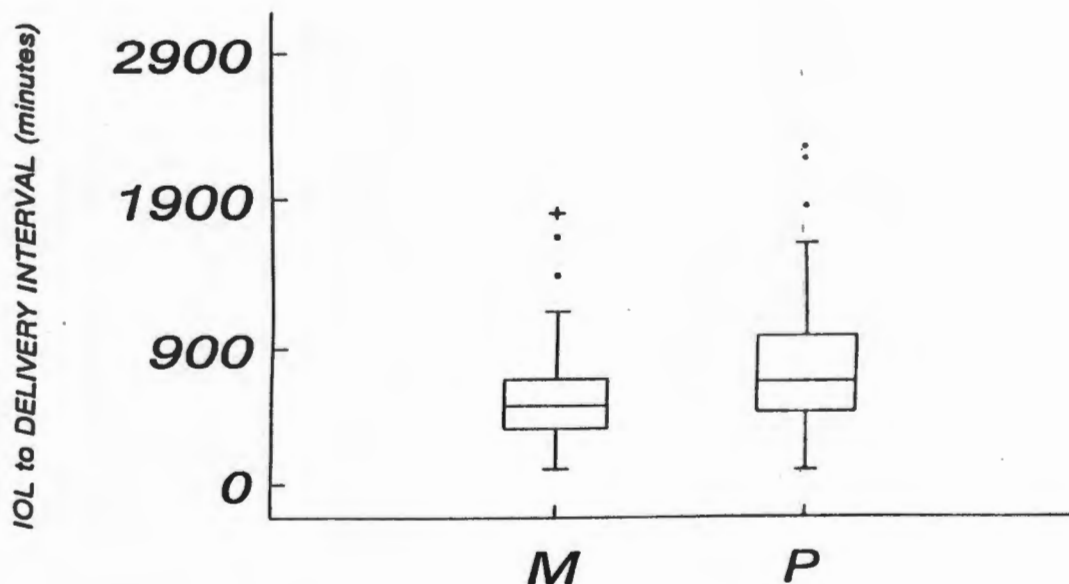


HPT - All hypertensive disease, including pre-eclampsia and chronic hypertension, DM - Diabetes Mellitus, PD- Post dates, IUGR- Intrauterine growth restriction, PPOH - Poor past obstetric history, Other - included Rhesus disease, previous pulmonary embolus, unexplained polyhydramnios at term.

Graph 3.1: Primary indication for induction of labour with misoprostol and prandin gel.

The use of misoprostol resulted in a significantly higher delivery rate within 12hrs than prandin gel. One hundred and thirty six patients (80%) who receive misoprostol and 91 patients (66,9%) who received prandin gel delivered within 12 hours of receiving the drug. ($P < 0.001$ OR 3,47 CI 2,09 to 5,79).

The mean overall IOL to delivery interval was also significantly reduced with the use of misoprostol (9hr13 SD = 5hr 53 vs 12hr18 SD = 6h 22) with prandin gel. ($P < 0.001$) (Graph 3.2)



Graph 3.2. Box and whisker plot showing the distribution of IOL to delivery intervals with misoprostol and prandin gel.

One hundred and eighteen patients achieved a vaginal delivery with misoprostol and 112 with prandin gel. There was no difference in the overall caesarean section rate between the two drugs. The caesarean section rate was 30.6% with misoprostol and 34,1% with prandin gel. (Table 3.2)

Table 3.2. Mode of delivery with misoprostol and prandin gel.

	<u>MISOPROSTOL</u> <i>n</i> = 170	<u>PRANDIN GEL</u> <i>n</i> = 170	Significance
Normal Vaginal delivery	111 (65.3%)	100 (58.8%)	NS
Instrumental Vaginal Delivery	7 (4.1%)	12 (7.1%)	NS
Caesarean Section	52 (30.6%)	58 (34.1%)	NS

Data is expressed as number (percentage)

Indications for caesarean section are shown in Table 3.3. The caesarean section rate for failed IOL was significantly lower for misoprostol (2.9%) than for prandin gel (8.2%) ($P < 0.05$), as was the caesarean section rate for failure to progress (0% for misoprostol vs 2.9% for prandin gel) ($P < 0.05$). However misoprostol resulted in a significantly higher incidence of caesarean section for fetal distress, 21.8% vs 10.6% for prandin gel. ($P < 0.01$).

Nineteen of the 37 patients in the misoprostol group who had a caesarean section for fetal distress, had a cord pH performed. Eleven of these had a $\text{pH} \leq 7.20$. Seven in the prandin group of 18 who had a caesarean section for fetal distress had a cord pH performed of which 2 were ≤ 7.20 . There was no particular indication for IOL that gave a higher propensity for a caesarean section for fetal distress. The incidence of fetal distress associated with tachysystole or hyperstimulation was similar with both drugs.

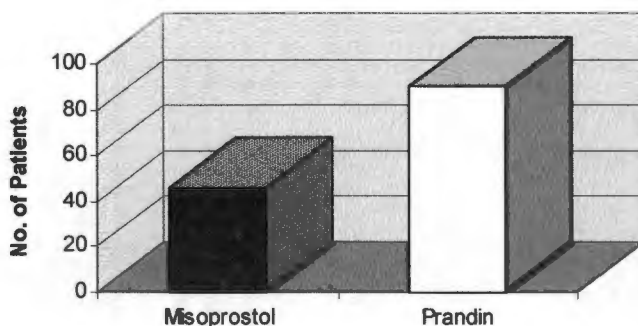
Table 3.3. Indications for caesarean section.

	<u>MISOPROSTOL</u> <i>n</i> = 170	<u>PRANDIN</u> <i>n</i> = 170	Significance
Failed IOL	5 (2.9%)	14 (8.2%)	P < 0.05 OR = 2.96 CI 0.97 to 9.66
Failure to Progress	0	5 (2.9%)	P < 0.05 OR = 0.0 CI 0.00 to 0.16
Cephalo-Pelvic Disproportion	8 (4.7%)	15 (8.8%)	NS
Fetal Distress	37 (21.8%)	18 (10.6%)	P < 0.05 OR = 2.35 CI 1.23 to 4.52
Other *	6 (3.5%)	2 (1.2%)	NS

Data expressed as number (percentage)

* 'Other' in misoprostol arm included 5 severe pre-eclampsics and 1 cord presentation, and in prandin arm, 1 severe pre-eclamptic and 1 undiagnosed breech presentation.

Significantly fewer patients who received misoprostol required a second dose of the drug: 39 (22.9%) patients as opposed to 55 (32.4%) patients who received prandin gel. (P = 0.05) Oxytocin was used to augment labour in only 46 (27%) of those receiving misoprostol as opposed to 90 (52.9%) patients who received prandin gel. (P < 0.001 OR 0.33 CI 0.2 to 0.5).(Graph 3.3)



Graph 3.3. Graph showing the number of patients who received oxytocin augmentation for delayed progress in labour.

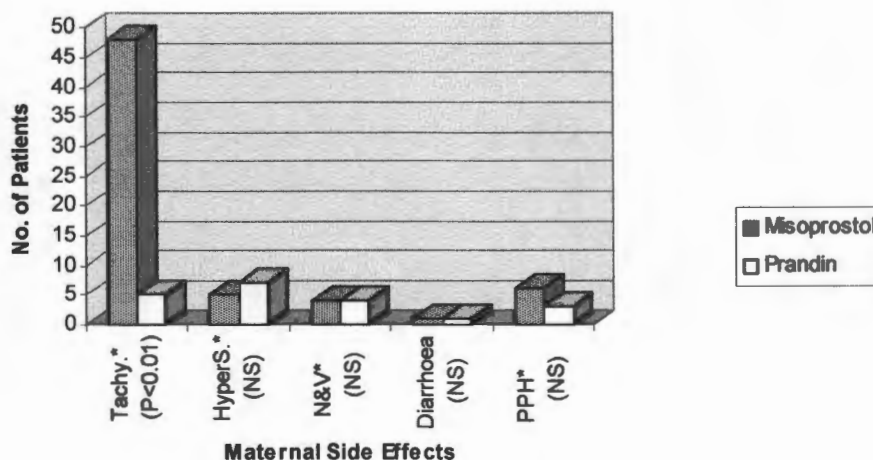
Maternal side effects are shown in Graph 3.4. Tachysystole occurred in 48 patients (28.2%) who received misoprostol. This was significantly more than in the prandin group where only 26 patients (15.3%) had this complication. ($P < 0.01$ OR 2.18 CI 1.24 to 3.85) The concomitant use of oxytocin did not appear to increase the incidence of tachysystole in patients who received misoprostol. The tachysystole did not appear to be related to the number of doses of drug used. Twenty seven percent of the patients with tachysystole in both groups had two doses of the induction agent. Hyperstimulation occurred similarly in the two groups (5 patients in the misoprostol arm and 7 in the prandin arm).

Maternal side effects of nausea, vomiting, diarrhoea and fever occurred very seldom and were no different in the two groups. One patient in the misoprostol arm developed a pyrexia. This was associated with clinical signs of chorioamnionitis. The incidence of a post partum haemorrhage was similar with the two drugs: 6 patients (3.5%) in the misoprostol arm and 3 patients (1.8%) in the with prandin gel arm.

Placental abruption occurred during induction of labour in 4 patients who received misoprostol. The indications for IOL in these four cases were: gestational proteinuric hypertension (GPH), post dates, polyhydramnios of unknown cause and diabetes mellitus. Two of these patients had associated tachysystole. All 4 patients were delivered by caesarean section. Two neonates had a cord pH < 7.2 but all had normal

Apgar scores and did not require neonatal resuscitation or admission to the Neonatal Intensive Care Unit (NICU).

One patient, a known epileptic, who received misoprostol had an epileptic seizure during the course of the induction. The only significant complication in the prandin group was that of a patient with underlying severe GPH who developed pulmonary oedema during induction of labour. This complication was felt to be unrelated to prandin used.



Tachy. - Tachysystole, HyperS. - Hyperstimulation, N&V- Nausea and vomiting, PPH - Post partum haemorrhage.

Graph 3.4. Maternal Side Effects and Complications Experienced with the IOL Agents

Opiate and/or epidural analgesia was requested in 118 patients in the misoprostol group and 120 in the prandin group. This difference was not significant.

Meconium staining of the liquor was present at delivery in 10 Patients (5.9%) in the misoprostol arm and 11 patients (6.5%) in the prandin group. An Apgar score of < 7 at 5 minutes was present in 4 neonates in each group. Eight neonates were admitted to the Neonatal Intensive Care Unit. Four of these neonates were in the misoprostol group. (Table 3.4) All four were admitted with the diagnosis of asphyxia neonatorum

of which one neonate had an associated major congenital abnormality of the corpus callosum and a second had asphyxia secondary to meconium aspiration. The aetiology of the asphyxia in the remaining two neonates was uncertain. Both mothers had been induced for GPH but with appropriately grown infants. Episodes of tachysystole were noted during the course of labour but these were not associated with any fetal heart rate abnormalities. At birth both neonates had poor Apgar scores (3 at 1 minute and 6 at 5 minutes in the first, and 5 at 1 minute and 6 at 5 minutes in the second) and required significant neonatal resuscitation and subsequent admission to the NICU. Their subsequent neonatal course was uncomplicated and they were discharged from the NICU on day 2.

In the prandin group all four neonates admitted to the NICU had a clinical diagnosis of asphyxia neonatorum. In one neonate this followed a vacuum extraction and subsequent shoulder dystocia in a mother who was induced for GPH and developed pulmonary oedema at full dilatation. Two further infants developed fetal distress following induction of labour for GPH and intrauterine growth restriction. The fourth neonate delivered following an uneventful labour, induced for GPH. It was born with Apgar scores of 3 at 1 minute and 6 at 5 minutes and required resuscitation at birth and admission to the NICU. There were no perinatal deaths in either arm of the study.

Table 3.4. Perinatal complications and neonatal outcome

	<u>MISOPROSTOL</u> <i>n</i> = 170	<u>PRANDIN GEL</u> <i>n</i> = 170	Significance
Meconium Stained Liquor	10 (5.9%)	11 (6.5%)	NS
Apgar Score < 7 at 5 Minutes	4 (2.4%)	4 (2.4%)	NS
NICU Admission	4 (2.4%)	4 (2.4%)	NS

Data expressed as number (percentage of total deliveries)

3.5 DISCUSSION

Induction of labour leading to timely delivery is often indicated for maternal or fetal reasons in the term pregnancy. Vaginally administered prostaglandin E₂ (the currently recommended drug of choice) provides successful induction of labour (IOL) rates of between 30% to 80 % (Keirse, 1994b). It is an expensive drug that requires continuous refrigeration. The development of a more consistently effective drug is justified. The cost of health care is also an important issue and the investigation of medical practise that reduces spending while improving or maintaining effectiveness and safety is also very important.

This study investigated misoprostol's potential use as an alternative agent to prostaglandin E₂ in induction of labour at term.

This study shows that misoprostol is significantly more effective in achieving a vaginal delivery within 12 hours than prandin gel. The use of misoprostol also reduced the mean overall IOL to delivery interval by over 3 hours. These differences are clinically significant especially in high and medium risk patients in whom an expeditious vaginal delivery is often indicated. These findings are consistent with the published literature on misoprostol, where the reduction in mean induction to delivery interval compared to PGE₂ has ranged from 6 hours to 8,2 hours (Wing et al, 1995a; Wing et al, 1995b; Chuck and Huffaker, 1995; Varaklis et al, 1995).

The efficacy of the drug is also reflected in the lower caesarean section rates for failed induction of labour and failure to progress. Misoprostol resulted in complete failure to ripen the cervix to allow rupture of membranes in only 5 patients as opposed to 14 patients who received prandin gel.

The overall vaginal delivery rate with both drugs was however similar at approximately 70 %. This finding is consistent with the literature. Caesarean section rates for misoprostol appear to be comparable to Prostaglandin E₂ (Fletcher et al, 1994; Wing et al, 1995a; Wing et al, 1995b; Chuck and Huffaker, 1995; Varaklis et al, 1995). In this study however

there were significant differences in the indications for operative delivery between the two drugs. This cannot be compared with the literature as few studies discuss the specific indications for caesarean section.

The significant reduction in use of oxytocin associated with misoprostol confirms its oxytocic properties. This is clinically relevant, as the use of oxytocin has its own inherent risks and side effects. Its use also increases costs and the added discomfort and dangers of an intravenous infusion to the patient.

Twenty two percent of patients who received misoprostol had a caesarean section for fetal distress. This figure was twice as high as in the prandin group. Similar doubling of incidence was found in the cervical ripening arm of the trial. Prediction of those patients at high risk for fetal distress was not possible and the cause of this higher incidence is not clear. No particular indication for IOL placed the patient at higher risk of fetal distress. A second dose of the drug and the addition of oxytocin were also not shown to be risk factors. Transplacental passage of the drug to the fetus and its direct effect on the fetal neurological and cardiovascular systems is still unknown and hence a direct effect on the fetus cannot be excluded as a cause for this higher incidence of fetal heart rate changes.

Once again the presence of acidosis and/or hypoxia could often not be confirmed pre surgery in these patients due to the poor cervical dilation. Confirmation with umbilical cord pHs post delivery was also not always performed. A third of neonates who had a caesarean section for fetal distress and who had cord blood gas analysis, had normal parameters. This is probably a reflection of two important factors. Firstly, it is known that there is a high false positive rate with abnormal fetal heart rate (FHR) tracings for the detection of true fetal compromise (van Geign, 1996). Secondly, normal umbilical cord blood analysis may reflect in part the success of intrauterine resuscitation with maternal oxygen therapy and tocolysis that a number of these patients received. It must be reiterated that despite the knowledge that false positive FHR tracings occur, the clinician is obliged to respond to abnormal FHR changes if no other confirmatory tests are possible. As with the cervical ripening trial, no increased adverse fetal or neonate outcome was

noted despite this high caesarean section rate for fetal distress in the misoprostol arm. The sample size is however too small in this trial to confirm this with certainty.

The literature is consistent with this study in showing minimal fetal and neonatal complications with the use of misoprostol (Margulies et al, 1992; Sanchez-Ramos et al, 1993; Fletcher et al, 1994; Wing et al, 1995a; Wing et al, 1995b; Chuck and Huffaker, 1995; Varaklis et al, 1995; Wing and Paul, 1996; Mundle and Young, 1996). Only one study has shown an increased need for neonatal resuscitation at birth and a higher incidence of meconium staining of the liquor and meconium aspiration syndrome with misoprostol (Wing et al, 1995a) Caution must however be used in interpreting these results since even the combined study sizes would be too small to allow definite conclusions regarding neonatal morbidity and mortality. Further studies, specifically designed to address fetal outcome need to be performed to evaluate this issue.

The four patients who received misoprostol who suffered intrapartum abruption placentae are of concern. There were also two cases of abruptio placentae associated with misoprostol use in the cervical ripening arm of the trial. Analysis of pooled data on the incidence of abruptio placentae in these two trials show its association with misoprostol to be significant ($P < 0.05$) Other than one reported case in a descriptive study by Bugalho and co-workers, no other reports of this complication are found in the literature (Bugalho et al, 1995). Abruptio placentae is potentially life threatening to the mother and fetus and consequently its association with the use of misoprostol is alarming. The possible role of misoprostol in the pathogenesis of the abruptio placentae is uncertain and further investigation is needed to evaluate if this finding occurred by chance in this study.

Tachysystole was twice as common with misoprostol as with prandin gel. In this study its incidence was unrelated to any patient profile or number of doses of the drug given. Oxytocin had no enhancing effect on tachysystole when it was used together with misoprostol. It may be postulated that those patients experiencing tachysystole had an inherent sensitivity to this particular drug that was expressed as an increased frequency of contractions. The same lack of adverse fetal outcome associated with the tachysystole was noted in this trial as with the cervical ripening arm and the same conclusions are valid. The

higher incidence of tachysystole with misoprostol when compared to prostaglandin E₂ or oxytocin is a consistent finding in the literature (Margulies et al, 1992; Fletcher et al, 1994; Wing et al, 1995a; Wing et al, 1995b; Chuck and Huffaker, 1995; Varaklis et al, 1995; Mundle and Young, 1996). None of these trials showed it to be associated with any higher incidence of adverse fetal outcome.

In this study the dosage regime chosen was based on that suggested by the published literature at the time. It was empirical and based on experience with early pregnancy abortions. Labour was successfully induced in 131 patients with a 100 µg dose. A further 34 patients went into labour after 200 µg of misoprostol. Since embarking on this trial researchers have evaluated lower dosage regimes in an attempt to establish a more favourable efficacy to side effect ratio. This issue has particularly been addressed to see whether lower doses reduce the incidence of tachysystole. A summary of the current published literature, indicating doses used with resultant mean insertion to delivery intervals, need for oxytocin and incidence of tachysystole, is found in Table 3.5.

From the literature it appears that lower doses of misoprostol may reduce the incidence of tachysystole but the duration of labour is lengthened and the need for oxytocin augmentation increased. In the two studies by Wing and co-workers particularly addressing drug dosage, a reduction in dose from 50 µg 3 hourly to 25 micrograms 3 hourly reduced the vaginal delivery rate and lengthened the IOL to delivery interval (Wing et al, 1995a; Wing et al, 1995b). Tachysystole was reduced but there was no difference in the incidence of abnormal FHR patterns and there was an increased need for neonatal resuscitation.

Table 3.5. Selected published series of induction of labour in term pregnancies with misoprostol.

Author	No.	Dosing regime	Maximum dose (μg)	Insertion to delivery interval (hr)	Oxytocin required (%)	Incidence of tachysystole (%)
Author's series	170	100 μg q 4 hr	200 μg	9.1 \pm 5.9	27	28
Fletcher et al 1993	32	100 μg	100 μg	15.6 \pm 12.5	29	0.03
Fletcher et al 1994	32	100 μg	100 μg	21.8 \pm 29.3	22	9.4
Margulies et al 1992	33	50 μg	50 μg	6.8 \pm 4.4	not stated	17
Chuck and Huffaker 1995	49	50 μg q 4 hr	250 μg	11.4 \pm 5.9	23	2
Wing et al 1995	68	50 μg q 3 hr	300 μg	18.3 \pm 12.5	33.8	36.7
Sanchez-Ramos et al 1993	64	50 μg q 4 hr	600 μg	11 \pm 7.3	22	34.4
Mundle and Young 1996	111	50 μg q 4 hr	800 μg	12.6 \pm 9.8	19.8	not stated
Varaklis et al 1995	79	25 μg q 2 hr	50 μg	16.0 \pm 7.7	44.4	8.3
Wing and Paul 1996	261	25 μg q 3 hr	100 μg	23.5 \pm 14.5	51.4	11.2
	261	25 μg q 3 hr	200 μg	15.1 \pm 8	41.8	14.6
Wing et al 1995	138	25 μg q 3 hr	200 μg	23.4 \pm 14.5	45.7	17.4

A study by Wing and Paul (1996), addressed the optimal frequency with which the drug is given. They compared a dosage regime of 25 μg 3 hourly to 25 μg 6 hourly in 522 patients. They found a significantly shorter IOL to delivery interval with the 3 hourly regime, with less need for oxytocin augmentation. No difference was found in the caesarean section rate, the incidence of tachysystole or the fetal outcome. As yet no consensus exists regarding the dose or regime that gives the best benefit to least risk ratio.

CHAPTER 4

CONCLUSIONS

The two studies presented indicate that misoprostol is more efficient than prandin gel in inducing labour and achieving delivery in the term pregnancy. It results in delivery within 12 hours in 80% of patients and reduces the overall induction of labour to delivery interval by 25% when compared to prandin gel. There is a reduced need for oxytocin augmentation with the drug and a reduced caesarean section rate for failed induction of labour.

The drug is easy to insert vaginally, does not require refrigeration and is a fraction of the price of the standard preparation of prandin gel. Currently 100 µg of misoprostol (half a 200 µg tablet) costs 81 cents as opposed to the R87.00 of a single application of 1 mg prandin gel.

These advantages must be weighed against the potential adverse effects of the drug. These trials highlight the significant increase in the contraction abnormality of tachysystole as well as the higher caesarean section rate for fetal distress. The incidence of abruptio placentae found in these trials is a major adverse finding. Neither of these studies nor any of the numerically smaller ones in the literature are large enough to comment reliably on perinatal mortality or morbidity and this remains a major concern and precludes routine clinical use of the drug. Sufficient literature on the drug has now been published for a meta-analysis to be performed. The combined literature is however probably still not large enough to draw conclusions about fetal safety. Larger studies particularly designed to look at these issues are needed

The dosage regime used in these trials was effective but resulted in a high incidence of tachysystole. More recent research has suggested that lowering the dose to 50 µg or 25 µg may reduce this side effect but efficacy is also reduced.

A further confounding factor in the current method of usage of misoprostol is the vaginal insertion of the drug in tablet form. Inconsistency of absorption is probable, and the effects of such variable factors as vaginal pH, presence of blood, mucus or liquor are unknown. Fletcher and co-workers

initially crushed the tablet and mixed it in an inert gel. This was a significantly more effective induction agent than placebo (Fletcher et al, 1993). The production of such a commercial preparation is highly desirable but would probably negate a large amount of the current cost benefits. It would also mean safe and effective dosage regimes would have to be re-evaluated.

The trials presented both used the vaginal route of application of the drug. The oral route may however offer a number of potential advantages. It would negate all concerns about variable vaginal absorption. It would also allow use in the presence of ruptured membranes. Fewer vaginal examinations would probably be required which would reduce chances for ascending infection and make patient acceptability higher. No work has yet been done on oral use in the third trimester but more and more experience is being gained in first and second trimester abortions. This is an area for further investigation.

Hence in conclusion, misoprostol appears to be an effective drug that has significant potential as an efficient cervical ripening and induction of labour agent. However adverse effects on the mother and the fetus suggested by higher incidences of fetal heart rate abnormalities, tachysystole and abruption placentae have not yet been adequately researched and the drug cannot be advocated for general use.

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