THE ROLE OF MISOPROSTOL IN THE THIRD STAGE OF LABOUR.

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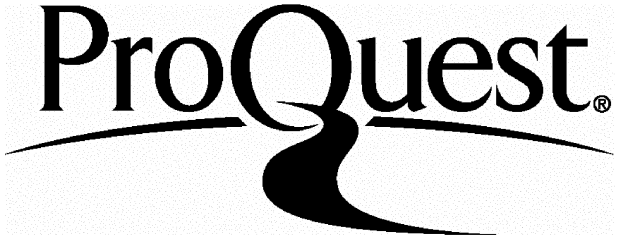

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Declaration

I hereby declare that this thesis has been written entirely by myself. The conception, design, data collection and analysis of each study and the writing up of every chapter in this thesis were done entirely by myself.

Chapter 2: I was involved in designing the Intrauterine pressure study. I conducted it at the National University Hospital, Singapore, where I was involved in patient recruitment. I carried out postpartum uterine activity measurements, calculation of uterine activity, data collection and analysis.

Chapter 3: I was involved in design, patient recruitment and conduct of both pilot studies. I carried out data collection and analysis of both studies.

Chapter 4: I was involved in the design and conduct of the randomised controlled trial, including patient recruitment. I collected the pre- and post-partum blood samples and patient questionnaires. I carried out all data collection and analysis.

Chapter 5: This study was designed and carried out entirely by myself, including its conduct, data collection and analysis.

Chapter 6: Postpartum uterine activity after rectal misoprostol administration was measured and calculated by myself at the National University Hospital, Singapore. I was involved in designing this study, and in collecting and analysing the data.

Randa Mohammed Nooh

ABSTRACT

Postpartum haemorrhage (PPH) is a leading cause of maternal death in both developing and industrialised countries. Its prevention is therefore of utmost importance. This thesis investigates the role of misoprostol, a prostaglandin E_1 analogue, in the prevention of PPH, when orally administered in the third stage of labour.

At first a physiological intrauterine pressure study was conducted to investigate the postpartum uterine response to different oral Misoprostol doses. Misoprostol was found to have a very fast onset and prolonged duration of action. A significant rise in uterine contractility was seen regardless of the dosage used. Two observational pilot studies were concurrently conducted; the first investigated the efficacy of 600 μgm of oral misoprostol for management of the third stage of labour, the second examined the efficacy of two lower doses; 400 and 500 μgm. The three groups were compared in terms of PPH rate (blood loss ≥ 500 mL), third stage events, and perceived incidence of side effects.

These studies were followed by a randomised-controlled trial comparing oral misoprostol to standard management of the third stage of labour. Patients were randomised to receive either 500 μgm of oral misoprostol, or the standard regimen of either syntometrine, syntocinon, or ergometrine, depending on maternal condition. This study had two primary end-points: the incidence of PPH, and the incidence and perceived severity of side effects in the two arms.

The main side effects of oral misoprostol were shivering and rise in temperature. Shivering occurred within 5 to 10 minutes of delivery, and lasted for 20 to 40 minutes. A significant rise in temperature was obvious within the first 15 minutes of drug administration, followed by a second significant rise occurring shortly after the onset of visible shivering.

The therapeutic value of Misoprostol was tested in the treatment of PPH due to uterine atony using the rectal route of administration, which has obvious advantages in PPH patients. The efficacy of 1000 μgm rectally administered misoprostol was investigated for the management of atonic PPH, unresponsive to conventional therapy. Misoprostol administration was quickly followed by firm contraction of the uterus and cessation of haemorrhage.

The series of studies described in this thesis prove that oral misoprostol may be effectively used for prevention of PPH, and may also play a role in its treatment. Misoprostol has great potential to reduce maternal mortality due to PPH, and may well be the perfect agent for use over the world.

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Glossary:

AH/PO region: Anterior Hypothalamic/Preoptic region

CCT: Controlled Cord Traction

CI: Confidence Interval

DHSS: Department of Health and Social Security

EUA: Examination Under Anaesthesia

ERPC: Evacuation of Retained Products of Conception

EBL: Estimated Blood Loss

FFIUPC: Fluid-Filled Intra Uterine Pressure Catheter

Hb: Haemoglobin

IM: Intramuscularly

IV: Intravenously

IOL: Induction of labour

IU: International Units

IUP: Intra-Uterine Pressure

IUPC: Intra-Uterine Pressure Catheter

MROP: Manual Removal of Placenta

MBL: Measured Blood Loss

NSAID: Non-Steroidal Anti-Inflammatory Drugs

OR: Odds Ratio

PG: Prostaglandin

PPH: Postpartum Haemorrhage

PIH: Pregnancy Induced Hypertension

RR: Relative Risk

SD: Standard Deviation

SEM: Standard Error of Mean

SVD: Spontaneous Vaginal Delivery

U: Units

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Chapter 1

Introduction

Background

The third stage is potentially the most hazardous part of labour for the parturient woman. The main risk is postpartum haemorrhage (PPH), which is a leading cause of maternal mortality and morbidity in both developing and industrialised countries. Up to 17 to 40% of maternal deaths occur as a result of PPH in some parts of the world (World Health Organisation (WHO), 1989; 1990; 1991). In the United Kingdom, an average of 5 deaths per year occur due to haemorrhage, representing 6.4 deaths per million maternities (Department of Health & Social security (DHSS), 1996).

The main strategy implemented to reduce postpartum bleeding is active management of the third stage of labour through administration of oxytocics; drugs that stimulate contraction of the uterus. The introduction of oxytocics for the prevention of PPH has been regarded as one of the most important advances in medical science. The intramuscular administration of Syntometrine® (a combination of 5 IU syntocinon with 0.5 mg ergometrine) is widely practiced in the developed world, and is the mainstay of active management of the third stage of labour. Prostaglandins also have oxytocic properties, and have been successfully used in several aspects of obstetrics.

Prophylactic use of oxytocics in the third stage of labour is of particular relevance to obstetric practice in third world countries, where atonic PPH is a common event due to high multiparity, prolonged labour and fibroid uterus. Randomised trials and their meta-analysis have consistently confirmed that active management of the third stage of labour reduces the incidence of PPH by about 30 to 40% compared to placebo, and the need for further oxytocic administration from 30% to 6%. The amount of postpartum blood loss, the length of the third stage, and the need for blood transfusions are all reduced

(Prendiville *et al.*, 1988 a, b; Prendiville & Elbourne, 1989; Prendiville & Elbourne, 1993 a, b, c; Renfrew *et al.*, 1995).

Active management of the third stage of labour is not a universal practice. In many parts of the world, the routine use of oxytocics is not a practical option for several reasons; firstly oxytocic agents in current use are not stable at high temperatures and require refrigeration to preserve their effectiveness, which represents an important hindrance to their use in temperate climates. Secondly, the routine use of Syntometrine requires prior knowledge of the patient's blood pressure status, which is not always the case in many parts of the world. Thirdly, the expense of syntometrine is quite high, and it is not affordable in many developing countries. Finally, the procedure is invasive, requiring a clean needle and syringe, which is an important consideration in view of the rising incidence of infections, such as hepatitis B, C, AIDS (Acquired Immuno-Deficiency Syndrome), and other blood borne diseases in many parts of the world.

In developing countries, refrigeration of drugs may be inadequate and access to a skilled birth attendant who is able to give an injection may not be possible, especially in rural areas. The high incidence of pregnancy anaemia and the inadequacy of blood transfusion services make it extremely vital to prevent avoidable loss of blood. Furthermore, It is of utmost importance to minimise the use of blood transfusions in developing countries since it is a major risk factor for transmission of Human Immunodeficiency virus (HIV) infection.

The use of ergometrine-containing preparations in the management of the third stage of labour is, however, associated with several drawbacks. Their advantages must be considered together with their rare but serious

hypertensive properties and gastrointestinal side effects, in the form of nausea and vomiting, which reduce their acceptability. Maternal death from cardiac arrest (DHSS, 1975) and intracerebral haemorrhage (Ringrose, 1962) have been attributed to ergometrine, as have non-fatal cases of cardiac arrest and myocardial infarction (Browning, 1974). Syntometrine is contraindicated in women with high blood pressure in pregnancy, and therefore an estimated 15% of parturient women are denied its benefit in the third stage of labour (Beisher & Mackay, 1986).

The side effects associated with the use of oxytocics, their parenteral administration, and their strict storage requirements has prompted scientists to search for other alternatives for the management of the third stage of labour. This alternative has to be an effective, inexpensive, oral agent, which could be used in both developed and developing countries at a population level, even in areas where refrigeration and trained personnel are not available.

At first, prostaglandins seemed to be the appropriate alternative for prophylaxis against PPH in the third stage of labour. Prostaglandin agents possess strong uterotonic features that have been utilised in obstetric practice for more than two decades. They are widely used for cervical ripening, induction of labour, and induction of abortion. Prostaglandins are effective in the management of intractable PPH (Schering, 1989), and, despite a lack of randomised trials, are recognised to be superior to oxytocin and ergometrine in that respect (Prendiville & Elbourne, 1989).

Unlike other oxytocics, prostaglandins are not hypertensive, and because of their strong uterotonic features and superiority in the management of PPH, they appeared to be ideal agents for prophylactic use in the third stage. Clinical trials assessing the efficacy of prostaglandins in the third stage of

labour have reported that both blood loss and the length of the third stage were reduced when compared with Ergometrine. However, most of the prostaglandins investigated had to be administered parenterally, intramyometrially, or by other routes e.g. intra-umbilically, which considerably reduces their acceptability as a routine prophylactic measure (Kerekes & Domokos, 1979). Prostaglandins were also found to have several other disadvantages; they are expensive, unstable at high temperatures, and are associated with potentially serious side effects, such as gastrointestinal symptoms, pyrexia, elevated blood pressure, dyspnoea and pulmonary oedema. Consequently, they are contraindicated in women with cardiovascular or pulmonary disease because of their potential hypertensive and bronchoconstrictor effects (Hankins *et al.*, 1988).

Misoprostol (Cytotec®, Searle Pharmaceuticals, Skokie, Illinois, USA) is a prostaglandin E_1 analogue, that is registered for the treatment and prevention of peptic ulcer disease. It has attracted worldwide attention in recent years because of its strong uterotonic features. Clinical trials have established its efficacy in surgical and medical induction of abortion, cervical priming, induction of labour, and mid-trimester termination of pregnancy. Misoprostol is rapidly absorbed after oral ingestion, and maintains its activity for prolonged periods at room temperature. It may therefore be a promising alternative for third stage management, because of its advantages, such as its low cost, its availability in tablet form that could be orally administered, and its demonstrated effectiveness as a uterotonic agent in various obstetric conditions.

At this stage, however, it is still important to investigate whether misoprostol is as effective as other oxytocics in prophylactic management of the third stage of labour and the prevention of PPH. This thesis investigates the role of

misoprostol in the management of the third stage of labour. The project began with a physiological study examining contractility of the puerperal uterus by measuring intrauterine pressure changes in response to different doses of orally administered misoprostol. Concurrently, an observational pilot study was conducted to examine the efficacy of a 600 μgm dosage of oral Misoprostol for third stage management on 237 patients. This was followed by a second pilot study (dose-finding and side effects study) to examine the efficacy of two further oral Misoprostol doses (500 and 400 μgm), and to compare patients' perception of associated side effects of the three dosages.

The results of the intrauterine pressure study and the two pilot studies were very encouraging, and the decision was made to conduct a large randomised controlled trial comparing the efficacy of oral Misoprostol to the current policy of third stage management using other known oxytocics. A dose of 500 μgm oral misoprostol was chosen to be used in the randomised trial subsequent to the dose-finding study, which established this dosage to be effective with minimal side effects.

Both pilot studies and the intrauterine pressure study revealed that the major side effects to oral misoprostol in the third stage of labour were shivering and pyrexia. Consequently, a small study was conducted to further investigate these two side effects in a sub-sample of women recruited to the randomised trial. A final study was conducted to examine the efficacy of rectally administered misoprostol in the management of atonic PPH, not responsive to conventional treatment.

1.1. THE THIRD STAGE OF LABOUR

1.1.1. Physiology of the third stage of labour

The third stage of labour is the stage of separation and expulsion of the placenta. It begins immediately after delivery of the infant and ends with the delivery of the placenta and fetal membranes. The third stage of labour involves hormonal and myometrial changes, in addition to mechanical or active forces, that combine to achieve the expulsion of the placenta and membranes, and control of bleeding. Postpartum haemostasis is achieved by a combination of factors that include contraction and retraction of the myometrium, vasoconstriction of blood vessels, and thrombosis.

Hormonal changes in the third stage of labour involve both oxytocin and prostaglandins. At the end of pregnancy, there is a marked rise in the concentration of oxytocin receptors in the myometrium, which leads to an increased sensitivity to oxytocin. A small increase in the concentration of circulating oxytocin in maternal blood is therefore sufficient to induce uterine contractions. Oxytocin is also thought to lead to stimulation of prostaglandin synthesis through receptors in the decidua. Prostaglandins, in turn, induce further contractions, soften the cervix, induce gap-junctions and sensitize the myometrium further for oxytocin, thereby leading to progressive cervical dilatation. Rupture of the membranes at the end of the first stage of labour, also leads to a further increase in prostaglandin synthesis (Husslein, 1985).

The level of oxytocin in the maternal circulation reaches a peak during the second stage of labour, then gradually falls to below first stage levels during the third stage (Dawood *et al.*, 1978). The increase in endogenous oxytocin concentration during the first and second stages is probably due to its

increased release through the maternal posterior pituitary gland. Fetal oxytocin is also thought to contribute to the rise in oxytocin levels in the maternal plasma (Thornton *et al.*, 1988).

Fuchs *et al.* (1991) investigated the pattern of oxytocin secretion among 32 parturient women in spontaneous labour. They reported that, during spontaneous labour, oxytocin was secreted in discrete "pulses" of short duration and increasing frequency. Blood samples were collected at one-minute intervals for 30 minutes, by a method that minimised degradation by plasma oxytocinase, and a highly specific antibody was used for the radioimmunoassay. The frequency of the oxytocin pulses was significantly higher during labour than before the onset of labour. The mean pulse frequencies per 30 minutes before labour was 1.2 (± 0.54), during the first stage was 4.2 (± 0.45), and during the second and third stages of labour was 6.7 (± 0.49). Mean durations of these pulse in the three groups were 1.2 (± 0.20), 1.9 (± 0.28), and 2.0 (± 0.26) minutes, respectively. The amplitudes of these pulses were variable with no significant differences between the groups, most of them being around 1.0 microU/mL. Gibbens and Chard (1976) confirmed that oxytocin was released in a series of "spurts" during labour, the frequency of which increased with the progress of labour, reaching a maximum in the second stage, and achieving peak levels of about 2 to 5 microU/mL.

Husslein *et al.* (1983) investigated plasma concentrations of oxytocin and prostaglandins before and after spontaneous labour. They measured the concentrations of oxytocin, PGE, PGF, and the metabolite 13,14-dihydro-15-keto-PGF_2 alpha (PGFM) in the maternal plasma. Serial blood samples were obtained at full cervical dilatation, and at 5, 30 and 120 minutes postpartum. Prostanoid levels were also measured in serial samples of umbilical cord blood

taken from the placental end. At full dilatation, plasma PGFM, but not PGE or PGF, was significantly raised over control values. The concentrations of PGF and PGFM were maximal just before or at the time of placental separation (5 min. postpartum), and twice the level at full dilatation. Its level then decreased but at a slower rate than the metabolic clearance rates. This indicates that considerable PGF production occurs in the decidua and myometrium in the early postpartum period. Prostanoid concentrations in umbilical cord blood was found to rise rapidly soon after delivery, which suggests that the surge of prostaglandins 5 minutes postpartum originates in the placenta, and contributes to uterine contraction and placental separation and expulsion. Plasma oxytocin was significantly raised over pre-labour values at full cervical dilatation, and during the third stage, but dropped to control levels 30 minutes postpartum. A marked increase in plasma oxytocin was seen among women who had received oxytocin infusions, and the PGFM concentrations were maintained at a higher level than among those who had not received oxytocin.

Thornton (1988) compared plasma oxytocin levels during natural and active management of the third stage of labour, and reported that a rise in plasma oxytocin is required for a normal third stage and uneventful delivery of the placenta. The concentration of plasma oxytocin was measured in serial samples obtained from 25 women, during the late second stage and throughout the third stage of labour. Ten women received active management by intramuscular ergotamine and oxytocin, and 15 did not receive oxytocin. Blood samples were collected every 30 seconds for 15 minutes, starting at crowning of the fetal head. The mean plasma oxytocin concentration before delivery of the fetal anterior shoulder was comparable between the two groups. However, all the women receiving oxytocin showed a rapid and significant rise in plasma oxytocin concentration, from 3.1 (SD 2.0) pmol/L to 15.9 (2.7) pmol/L, after delivery of the fetal anterior shoulder and before

delivery of the placenta. The mean peak plasma oxytocin concentration was 30.5 (2.5) pmol/L, and all the women in this group delivered the placenta within the 15-minute sampling period. On the other hand, among women who did not receive oxytocin, six showed a significant increase in mean plasma oxytocin concentration from 3.2 (2.0) pmol/L before delivery of the fetal anterior shoulder to 6.4 (2.0) pmol/L after. The other nine women did not show an increase in oxytocin concentration (2.4 (3.1) pmol/L before and 2.2 (2.2) pmol/L after), and two women in this group had an abnormal third stage of labour; one having PPH, and one requiring manual removal of the placenta. The prophylactic use of intramuscular oxytocin in the third stage of labour was recommended to all parturient women, since it was difficult to predict which women will demonstrate a spontaneous rise in plasma endogenous oxytocin concentration.

Prostaglandins play an important role in human parturition; whether in labour, cervical dilatation, during delivery, or in placental separation (Casey & MacDonald, 1986; Kierse MJNC, 1983; Mitchell, 1986). Prostaglandins also play a major role in achieving postpartum haemostasis. Increased levels of prostaglandin production in the third stage of labour have been reported by various researchers (Zuckerman *et al.* 1978; Sellers *et al.* 1982; Ilancheran & Ratnam, 1990). Prostaglandin release in the third stage of labour occurs as a result of uterine contractions brought about by increasing levels of oxytocin, that reach their peak during the second stage of labour. However, available research indicates that the levels of metabolites of both prostaglandin E and F peak in the maternal circulation after, rather than before, birth (Sellers *et al.*, 1982; Husslein, 1983). This may explain why exogenous prostaglandin administration often ensures adequate uterine contractility and arrest of PPH when other measures fail.

All uterine tissues, the fetal membranes, and the placenta, have the ability to form prostaglandins from endogenous precursors in vitro. Among the prostaglandins synthesised by the pregnant uterus are PGI_2, PGD_2, and to a lesser extent PGE_2, which are vasodilators and potent inhibitors of platelet aggregation. The concentration of PGI_2 and its metabolites increases in the plasma of pregnant women near term, rises significantly during labour, and reaches below pre-labour levels within two hours after delivery (Kimball, 1983; Seed *et al.*, 1983). Its vasodilator properties ensure adequate blood supply to the placenta and fetus during uterine contractions by keeping the blood vessels dilated to maintain their blood flow. As soon as the infant is delivered, PGI_2 has no further role to play, so its production ceases, and blood levels fall.

During delivery, synthesis of endogenous prostaglandin F dramatically increases, reaching a maximum at the time of placental separation. The most important prostaglandins that participate in postpartum haemostasis are $PGF_{2\alpha}$ and TXA_2, the concentrations of which increase markedly during the third stage of labour. $PGF_{2\alpha}$ induces myometrial contractions thereby squeezing the uterine blood vessels, but has little or no effect on platelet aggregation (Toppozada, 1979). On the other hand, TXA_2, which acts as a powerful vasoconstrictor, facilitates rapid and irreversible platelet adhesion, promotes clotting, and closes down the open sinuses following placental separation (Zuckerman *et al.* 1978; Ilancheran & Ratnam, 1990).

Karim & Devlin (1967) were the first to report the presence of PGE_2 and $PGF_{2\alpha}$ in the amniotic fluid. The concentration of PGE was found to increase in the amniotic fluid in late pregnancy and during labour, while $PGF_{2\alpha}$ increased only during labour. Neider & Augustin (1983) reported that amniotic fluid PGE and PGF remained unchanged until about 34 weeks of

pregnancy, and then increased exponentially. PGF levels were found to increase 13 times its original value following cervical dilatation, while the PGE equivalent remained unchanged.

Sellers *et al.* (1982) demonstrated raised prostaglandin levels in the third stage of labour, and reported that metabolite levels were highest 5 minutes after delivery than at placental separation. Serial samples of maternal peripheral plasma were obtained to measure the concentrations of 13,14-dihydro-15-keto-prostaglandin F (PGFM) and oxytocin during the three stages of labour, and in the immediate postpartum period. The level of PGFM was found to increase as labour progressed, reaching a peak just before placental separation. Its mean plasma concentration in the second stage of labour was significantly higher than that in the first stage (p-value < 0.01). Similarly, the mean concentration 5 minutes after delivery, before expulsion of the placenta, was significantly greater than that in the second stage of labour (p-value < 0.01). There was no significant difference between mean PGFM concentration at placental separation and that at 5 minutes after delivery or in the second stage of labour. Two hours after delivery of the placenta, PGFM levels fell to values of the first stage of labour.

Norman and Reddi (1990) suggested that PGE_2 was the principle prostaglandin responsible for the onset of labour, while $PGF_{2\alpha}$ was responsible for the progress of labour. Another view was presented by Macdonald & Casey (1993), who argued that the accumulation of prostaglandins in the amniotic fluid was an after-effect of labour that was not indicative of their role in parturition. They estimated the concentrations of PGE_2, $PGF_{2\alpha}$, and PGFM in the forebag and upper compartment of the amniotic sac during labour. A marked increase in these prostaglandins was found only in the forebag. The production and entry of prostaglandins into the amniotic fluid was therefore

thought to occur during, and not before the onset of labour, from the lining of the forebag or decidua parietalis; which is thought to be the principal site of prostaglandin production.

Noort *et al.* (1989) investigated the changes in plasma levels of $PGF_{2\alpha}$ and PGI_2 metabolites at and after delivery in 10 women in labour, at term. Serial blood samples were obtained from each woman: hourly until full dilatation, at full dilatation, immediately after delivery of the fetal head, and immediately before delivery of the placenta. After expulsion of the placenta, samples were obtained at 5, 10, 15, 30, and 45 minutes, and then every hour up to 6 hours postpartum, then every 6 hours up to 48 hours. All women in the study showed an increase in PGFM levels during the first stage of labour, reaching a maximum at full dilatation, during which the levels were significantly higher than at any time during the first stage (p-value < 0.005). At delivery of the fetal head, the levels of PGFM was significantly higher by an average of 30%, than at full dilatation (p-value < 0.05). At placental separation, PGFM levels rose further to levels twice as high as at full dilatation (mean 853 pg/mL compared to 378 pg/mL). After placental separation, the concentration of PGFM increased further and the highest level was observed within 5 minutes of separation of the placenta, in all women in the study. After that, the level of PGFM rapidly declined, such that after three hours of placental separation, it was significantly lower than that measured at the onset of labour (p-value $<$ 0.01). This study confirms that peak PGFM levels are reached after delivery, and that the level of prostaglandin metabolites are highest at placental separation, than at any other time in labour. The increase in PGFM levels at placental separation was thought to result from an increase in synthesis of all primary prostaglandins consequent to cellular disruption and necrosis at the placental implantation site, or at the site of detachment of the fetal membranes. PGFM levels rapidly decline within 10 minutes of placental separation, which

suggests that the major source of this metabolite is removed with the delivery of the placenta. It is thought that the peeling off of the fetal membranes in particular, is the main source of the surge in PGFM levels, which explains its very rapid decline.

With regard to myometrial changes in the third stage of labour, it was found that the cytotrophoblasts directly in contact with the maternal decidua produce a modified fibronectin, known as *oncofetal fibronectin.* This fibronectin acts as a "trophoblast glue" that mediates implantation and placental attachment in the uterus throughout gestation, and is also thought to facilitate the separation of chorion laeve from decidua parietalis at delivery. The levels of oncofetal fibronectin in the cervical and vaginal secretions are seen to increase in women in labour, both at term and preterm (Feinberg *et al.*, 1991; Lockwood *et al.*, 1991). Prostaglandins and other mediators of the inflammatory process are also produced by the amnion and chorion laeve, and decidua, and are also thought to facilitate the separation and delivery of the fetal membranes.

With respect to mechanical changes, uterine contractions continue after delivery, at a reduced frequency but at a higher intensity, even exceeding that of contractions of the first stage of labour. This is accompanied by an elevation of intrauterine basal tone. Intrauterine pressure continues to rise rhythmically, which diminishes myometrial blood flow by mechanical compression of the blood vessels. These high amplitude contractions along with the rise in intrauterine pressure in the immediate postpartum period help in achieving clinical haemostasis and decreasing uterine size. The total amount of postpartum blood loss increases as total uterine activity in the third stage of labour decreases (Chua *et al.*, 1996).

As the infant is delivered, the uterine muscles contract and retract spontaneously, and the uterus, along with the upper segment decrease significantly in size. When delivery of the placenta is imminent, the uterus rises in the abdomen, and becomes globular in configuration, indicating that the placenta has separated and has entered the lower uterine segment. This is accompanied by a gush of blood and/or "lengthening" of the umbilical cord. Placental separation ordinarily occurs within a few minutes after delivery, usually starting in a place other than the periphery of the placenta, which is thought to be the most adherent portion. Some degree of placental separation may occasionally begin before the third stage of labour, which accounts for certain cases of antepartum haemorrhage or fetal distress that occur just before delivery.

By the time the infant is delivered, the uterine cavity is nearly obliterated. Contraction and retraction of the myometrium reduces uterine volume. The walls of the uterus above the lower segment become thick, and the fundus lies just below the level of the umbilicus. Contraction of the uterus to a small size causes a *shearing* effect, which tears the decidual septae and separates the placenta (Herman *et al.* 1993). The sudden decrease in uterine size is accompanied by a reduction in the area of the placental implantation site. Since the placenta is incompressible, it has to accommodate itself to the reduced area, so it increases in thickness and is forced to "buckle" because of its limited elasticity. The resulting tension causes the weakest layer of the decidua to give way, and cleavage takes place at that site. As separation of the placenta proceeds, a haematoma forms between the separating placenta and the remaining decidua, which accelerates the process of cleavage (Engelbrecht *et al.*, 1979).

If the placenta is implanted at the fundus, the "central" type of placental separation occurs. The retroplacental haematoma pushes the placenta through its central portion towards the uterine cavity. The placenta is weighed down with the haematoma, becomes inverted, and then descends. As the surrounding membranes are still attached to the decidua, the placenta drags the membranes along, and they peel off. Consequently, the sac formed by the membranes becomes inverted, and the placenta draws the membranes after it, covering its raw surface. The retroplacental haematoma either follows the placenta or is found within the inverted sac. This process is known as the "Schultz mechanism" of placental expulsion. Blood from the placental site pours into the inverted sac, and does not escape externally until after extrusion of the placenta.

When the leading edge of the placenta separates first, the mechanism of placental expulsion is known as the "Matthews-Duncan mechanism". In this case, separation of the placenta first occurs at the periphery, which results in the blood collecting between the membranes and the uterine wall, then escaping from the vagina. This is followed by the placenta descending sideways into the vagina. The maternal surface is the first to appear at the vulva, and the placenta is delivered with its raw surface exposed.

The membranes usually remain in situ until separation of the placenta is nearly completed, after which they are peeled off the uterine wall, partly by pressure exerted by the uterine walls through further contraction of the myometrium, and partly by traction exerted by the separated placenta. After having separated from its implantation site, the placenta usually lies in the flaccid lower uterine segment or in the upper portion of the vagina. It is then expelled by an increase in abdominal pressure. After expulsion of the placenta, or end of the third stage, the body of the uterus forms an almost solid mass of muscle.

The anterior and posterior walls of the uterus, each measuring 4 to 5 cm in thickness, lie in close apposition, and the uterine cavity is almost obliterated.

Physiological control of postpartum bleeding occurs by contraction and retraction of the interlacing myometrial fibres surrounding the blood vessels supplying the placental implantation site, which is of utmost importance for minimising blood loss during and after expulsion of the placenta. During this process there is some bleeding from the maternal sinuses and the placental bed. Any impairment or failure in the contraction and retraction mechanism or incomplete placental separation results in continuation of bleeding from the maternal sinuses and PPH.

Goto (1984) classified placental separation and expulsion ultrasonographically into three types; I, II, and III. In Type I, the placenta smoothly separates from its bed and slides out soon after the delivery of the fetus, usually with the first or second after-pains. This is the most common method of placental expulsion (53%), and is considered to be the safest, since it is associated with the least blood loss, and the shortest third stage duration. In Type II, separation of the placenta begins at the periphery, and progresses with each recurring uterine contraction. Blood loss is continuous and greater, and expulsion of the placenta may be delayed. In Type III, separation of the placenta starts in the central part, and progresses with the formation of a retroplacental haematoma, which results in an increase in placental size. Blood loss and duration of the third stage in this type are moderate.

Herman *et al.* (1993) reported that, when not influenced by routine use of oxytocics, the normal third stage of labour could be divided into four phases. The first is a latent phase, characterised by thinning of the placental site and thickening of the surrounding myometrium. The second is a contraction phase,

during which thickening of the placental site occurs (from < 1 cm to > 2 cm). The third is a detachment phase, in which the placenta detaches and completes its separation, and the final phase is the expulsion phase, which ends with the placenta sliding out.

The duration of the third stage of labour is normally around 5 to 15 minutes, even without mechanical or pharmacological assistance. The main complications associated with the third stage of labour, which greatly increase maternal morbidity and mortality, are retention of the placenta and PPH. When the third stage lasts over 15 minutes, this usually indicates retention of the placenta, which is the term applied to failure of expulsion of the placenta. If blood loss exceeds 500 mL this indicates primary PPH. Excessive blood loss after expulsion of the placenta suggests the possibility of uterine atony, which is the most common cause of postpartum bleeding.

1.1.2. Management of the third stage of labour

Active management of the third stage of labour is a wide term that is perceived differently by different people. It is mainly practiced in industrialised countries, and is approached by the administration of an oxytocic agent; such as oxytocin (Syntocinon®; Sandoz Pharmaceuticals, Camberley, Surrey, UK), Ergometrine, or Syntometrine, to speed up expulsion of the placenta, together with early clamping of the cord, and delivery of the placenta by cord traction. The most common oxytocic used is syntometrine, which is intramuscularly administered. Prostaglandins have also been successfully used for management of the third stage of labour, and will be discussed in a separate section.

There is strong evidence of the benefit of active management of the third stage of labour, which has been confirmed by meta-analysis of various randomised-controlled trials. Tables 1.1 and 1.2 demonstrate different PPH rates in published randomised trials of third stage management.

Oxytocic administration along with cord traction shortens the duration of the third stage to within 5 minutes in nearly 90% of cases, and within 15 minutes in 97% of cases (Hibbard, 1964). Routine use of syntometrine in the third stage reduces the incidence of PPH from around 18% to 5%, the length of the third stage of labour from 15 to 5 minutes, and the need for therapeutic oxytocics from 30% to 6% (Prendiville *et al.*, 1988 a, b; Prendiville & Elbourne, 1989; Prendiville & Elbourne, 1993 a, b, c). In a systematic review of controlled trials investigating active management of the third stage of labour, Prendiville *et al.* (1988 a) analysed data obtained from nine published reports in which an oxytocic drug was compared with either a placebo or no oxytocic. Routine use of an oxytocic agent was reported to reduce the risk of

PPH by about 40% (odds ratio (OR) = 0.57, 95% Confidence Interval (CI) 0.44 of 0.73), implying that for every 22 women receiving a prophylactic oxytocic, one PPH case could be prevented. When no oxytocic is used, the PPH rate reaches up to 15% if the length of the third stage exceeds 15 minutes, and nearly 30% if it exceeds 30 minutes (Hibbard, 1964).

Research into active management of the third stage of labour began in the thirties with the discovery of ergometrine (Dudley & Moir, 1935). However, historical references to the use of ergot by midwives appear as early as the 16th century. The first documented account for its use dates to 1808, when the American physician Dr John Stearns reported the use of "pulvis parturiens" as treatment of "lingering labour". Present day use of ergot compounds in obstetrics owes much to the pioneering work of Chassar Moir (1932), who discovered the most active oxytocic, ergometrine (Dudley & Moir, 1935). All Ergot alkaloids were found to possess two main properties; oxytocic and sympatholytic. Moir described the similar oxytocic effects of ergotoxine and ergotamine, which were thought to be the essential components of crude ergot for many years. Both were slow in action, with a latent interval of about 20 minutes after intramuscular administration, inducing strong uterine contractions that gradually increased in frequency, to merge in a prolonged period of uterine hypertonus, then slowly declining. The crude extract *ergot. liq.* was found to be much faster in action. Ergometrine was found to have the most active oxytocic properties, inducing uterine contractility within 7 minutes of intramuscular injection, and less than one minute of intravenous administration. However, its duration of action was found to be shorter than ergotoxine.

Ergometrine was found to induce a long-lasting uterine spasm, which made it unsuitable for use before delivery of the infant because of the danger of fetal

asphyxia or uterine rupture. Its benefit therefore lied in the prevention of postpartum and post-abortion bleeding. Its haemostatic properties were found to be derived from both a contractile effect on the myometrium, and a specific vasoconstrictor effect on uterine vessels.

The introduction of syntometrine, a combination of 0.5 mg of ergometrine and 5 units of oxytocin, was an important advance in obstetrics that refined the concept of prophylactic management of the third stage of labour. Syntometrine combined the speed of action of oxytocin with the sustained effect of ergometrine. Embrey (1964) established that the rapidity of action of intramuscular ergometrine was 7 minutes, intravenous ergometrine 40 seconds, and intramuscular syntometrine 2.5 minutes. By the eighties, the success of active management of the third stage of labour by intramuscular administration of the combination of ergometrine and oxytocin, in addition to controlled cord traction as mechanical assistance in delivery of the placenta, had been established (Heinonen & Pihkala, 1985). The mixture of oxytocin and ergometrine appeared to be the safest and most effective prophylactic against PPH (Elbourne *et al.*, 1988 a). The administration of syntometrine is now routinely practised in many units and, when given intramuscularly at the time of crowning of the head or delivery of the anterior shoulder, reduces both the incidence and severity of primary PPH.

In passive (expectant, physiologic or conservative) management, the cord is clamped relatively late (after 1 minute) and the placenta is delivered with the help of gravity and maternal effort. Oxytocics are only used if there is excessive bleeding. Other reported methods of physiological management include immediate infant suckling and/or nipple stimulation, which are thought to be safe alternatives to oxytocin (Kim *et al.*, 1986). In a randomised controlled trial investigating the effect of suckling immediately after birth on

the third stage, Bullough *et al.* (1989) reported that the frequency of PPH was lower in the suckling group than in the control group (7.9% and 8.4%, respectively). The mean blood loss was also slightly lower (258 mL and 256 mL, respectively), but neither results differed significantly. Irons *et al.* (1994) conducted a randomised controlled study comparing three groups; the first group received 15 min. of nipple stimulation (n = 6), the second group received routine syntometrine injection (n = 3), and the third group acted as controls (n = 5). Uterine pressure was higher during nipple stimulation (103 mm.Hg compared to 70.8 mm.Hg, p-value = 0.04). The duration of the third stage and blood loss were also reduced (20.3 min. compared to 12.3 min., and 257 mL compared to 166 mL, respectively) but was not statistically significant. Similar differences were also observed between women receiving syntometrine and the control group.

Many variations in the management of the third stage of labour have been reported, even a mixture of active and passive management regimens have been used. Each method has its advantages and disadvantages, which has created a major confusion in the literature. Review of the literature on management of the third stage of labour reveals two major types of studies; those that have investigated total active management of the third stage as a "package" of therapeutic interventions, and those that have investigated the value of specific pharmacological agents. During the past decade, however, conflicting reports have been seen, ranging from studies promoting the role and advantages of active management, to claims that routine active management increases rather than decreases maternal and neonatal morbidity. Some researchers have questioned the value of active management of the third stage of labour, arguing that it interferes with the natural physiological process of parturition (Dunn, 1966; Inch, 1985), and claiming that it may be associated with more disadvantages than physiological management (McDonald *et al.*,

1993). Furthermore, there has been a lot of pressure towards demedicalisation of labour in the last 20 years.

Ergometrine and oxytocin have been used for prophylaxis against PPH in different dosages and by various routes with varying success. Numerous studies have been conducted to investigate and compare the value of specific pharmacological agents used in the third stage of labour. Yuen *et al.* (1995) compared intramuscular syntometrine with syntocinon for the management of the third stage of labour, in a randomised double-blind prospective study on 1000 women with single pregnancies and vaginal deliveries. They advocated the superiority of syntometrine, which was found to reduce postpartum blood loss and was associated with a 40% reduction in the risk of PPH (OR = 0.60; 95% CI of 0.21 to 0.88) and the need for additional therapeutic oxytocics (OR = 0.63; 95% CI of 0.44 to 0.89). The duration of the third stage of labour was similar with the two drugs, but the incidence of manual removal of the placenta was higher with syntometrine (OR = 3.7; 95% CI of 1.03 to 12.5). Side effects from both drugs, such as nausea, vomiting, headache and hypertension, were uncommon.

Nordstrom *et al.* (1997) reported that intravenous oxytocin administered in the third stage of labour was associated with a 22% reduction in mean blood loss, and a 40% reduction in the incidence of PPH. In a double blind, randomised controlled trial on 1000 women undergoing vaginal delivery, patients received either intravenous oxytocin (Partocon 10 IU) (n = 513), or 0.9% saline solution (n = 487) for third stage management. A cut-point of over 800 mL was used to define haemorrhage. Oxytocin administration was associated with a significant reduction in mean total blood loss (407 compared to 527 mL), frequency of PPH (5.2% compared to 8.8%), further oxytocic therapy (7.8% compared to 13.8%), and postpartum Hb < 10 g/dL (9.7% compared to

15.2%). However, it was associated with a non-significant increase in the frequency of manual removal of the placenta (3.5% compared to 2.3%).

Other studies have investigated active management of the third stage of labour as a "package" of therapeutic interventions that included administration of an oxytocic agent and clamping and traction of the cord. The Bristol third stage trial was the first large randomised study to prove that active management reduced the incidence of PPH, the length of the third stage of labour, and the need for therapeutic oxytocics (Prendiville *et al.*, 1988 b).

In the Bristol third stage trial, active management of third stage of labour was compared with physiological management to investigate whether active management reduced the incidence of PPH, and their effects on fetal and maternal morbidity. Women were randomly allocated to receive either physiological (n = 849) or active (n = 846) management. In physiological management, no oxytocic was given, cord was not clamped until after delivery of the placenta, and no cord traction was applied. Active management comprised administration of a prophylactic oxytocic, cord clamping before placental delivery, and cord traction. Active management was received by almost all the allocated women (99%), and was very successful. In comparison, among women allocated to physiological management less than half of them actually achieved it (47.5%). A fifth (19.8%) of women allocated to the physiological group received prophylactic oxytocics, two fifths (39.6%) required cord traction, and the cord had to be clamped in over half of them (51.5%) before placental delivery. The incidence of PPH was 5.9% with active management, and 17.9% with physiological management. The OR of having PPH with physiological rather than active management was 3.13, 95% CI of 2.3 to 4.2). In the physiologically managed group, the third stage was longer (median 15 min. compared to 5 min.) and more women needed therapeutic

oxytocics (29.7% compared to 6.4%). When women who had been allocated to and received active management (n = 840) were compared with those who actually received physiological management (n = 403), active management still produced a lower PPH rate (OR = 2.4, 95% CI of 1.6 to 3.7). Active management of the third stage of labour was found to reduce the incidence of PPH, and shorten the third stage of labour. The Bristol third stage study demonstrated the benefits of active management of the third stage of labour as a therapeutic strategy "package", but did not investigate the value of a certain pharmacological agent for the prevention of PPH.

In the Salford third stage trial, Mitchell and Elbourne (1993) reported that syntometrine was more effective than syntocinon in the prevention of PPH, as part of active management of the third stage of labour. In a double-blind, randomised controlled trial, 230 women were allocated to receive syntometrine, and 231 to receive syntocinon, both intramuscularly (IM) with delivery of the anterior shoulder. There was a lower incidence of primary PPH > 500 mL in the syntometrine group (OR = 0.37; 95% CI of 0.16 to 0.85). The duration of the third stage in both groups was similar (difference in means 0.2 min.; 95% CI of -1.0 to 1.5), so was the need for manual removal of the placenta (OR = 1.21; 95% CI of 0.37 to 4.00).

Thilaganathan *et al.* (1993) compared active and physiological management of the third stage of labour among low risk women. Women were randomly allocated to receive either active management with syntometrine and controlled cord traction (CCT) (n = 103); or physiological management (n = 90), where the cord was not clamped and the placenta was delivered by maternal effort. There was no significant difference in estimated blood loss (median EBL = 200 mL versus 200 mL) or drop in haemoglobin between the two groups (p-value > 0.5), but the duration of the third stage was significantly

longer in the physiological group (p-value < 0.001). They reported that active management reduced the length of the third stage but did not specifically reduce postpartum blood loss among women at low risk of PPH.

Khan *et al.* (1997) reported that intramuscular administration of oxytocin and active delivery of the placenta by CCT resulted in a significantly lower incidence of PPH and retained placenta, and less need for additional therapeutic oxytocics. Women were randomly allocated to two groups; the first group received 10 units of oxytocin IM with delivery of the anterior shoulder, and the placenta was actively delivered by CCT (n = 827), while in the second group the placenta was delivered by maternal pushing (n = 821). The incidence of PPH was significantly lower in the CCT group (5.8% compared to 11%; OR = 0.50, 95% CI of 0.34 to 0.73). The incidence of retained placenta (≥ 30 minutes) was 1.6% in the CCT group and 4.5% in the minimal intervention group (OR = 0.31, 95% CI of 0.15 to 0.63). Significantly more patients in the minimal intervention group required additional uterotonic therapy to control haemorrhage (5.1% compared to 2.3%; OR = 0.44, 95% CI of 0.24 to 0.78).

Other alternative active management strategies include the use of intra-umbilical vein oxytocin, which was also associated with a short third stage duration and lowering of postpartum blood loss (Reddy & Carey, 1989; Dahiya *et al.*, 1995). Dahiya *et al.* (1995) reported that intraumbilically administered oxytocin reduced both the duration of the third stage and postpartum blood loss. Pregnant women were randomised into two groups of 50 each. The first group received 10 units of oxytocin diluted in 20 mL saline, through the umbilical vein immediately after cord clamping. The second group received oxytocin infusion 10 units in 250 mL of dextrose saline at a rate of 125 mL/hr., after delivery of the baby. Intraumbilical oxytocin was associated

with a statistically significant decrease in the duration of the third stage of labour (1.48 min. compared to 3.27 min.), and a lower drop in haemoglobin (1.2 g/dl compared to 1.96 g/dl) and haematocrit (3.88% compared to 7.20%).

In the quest to find the optimum oxytocic agent for prophylactic management of the third stage of labour, a report from Holland looked into the role of oral methylergometrine in the prevention of PPH in a series of three studies (De Groot, 1995; 1996). In the first study the pharmacokinetics and bioavailability of oral versus intravenous ergometrine and methylergometrine were investigated in men and non-pregnant women. There was an extreme inter-individual variation in bioavailability of methylergometrine and its oral administration did not appear to be the most reliable route for accurate dosing to prevent PPH. In the second study, the pharmacodynamic and pharmacokinetic effect of oral and intravenous methylergometrine on uterine contractility was investigated by means of intrauterine pressure measurement during menstruation. Oral methyl-ergometrine was found to have an unpredictable and late effect on uterine motility, which was presumed to be due to unpredictable bioavailability, in contrast to its fast and predictable effect following intravenous administration. The third study was a three-arm randomised trial in which three different third stage management strategies were compared. The first group of women received 0.4 mg of ergometrine maleate orally (n = 146), the second group received the standard oxytocin regimen of 5 IU intramuscularly (n = 78), and the third group received a placebo (n = 143). Compared to placebo, oral ergometrine was found to reduce blood loss by 5% (-5%; CI of –20 to +13%), while oxytocin reduced blood loss by 9% (-9%; CI of –26 to +12%). Results of the three studies indicated that ergometrine and methylergometrine tablets were unstable even when stored in refrigerated conditions. The pharmacokinetic and dynamic properties of methylergometrine were unpredictable, and it demonstrated no clinical

effect in reducing postpartum blood loss. Oral methyl ergometrine was therefore not an appropriate alternative to parenteral oxytocics for prophylactic management of the third stage of labour.

Despite the consensus among clinical trials proving the advantages of active management of the third stage of labour over physiological management, in terms of reducing blood loss, length of the third stage, and incidence of PPH, several problems remain. Certain complications have been attributed to the use of ergometrine, such as non-fatal cardiac arrest, coronary artery spasm, and myocardial infarction (Browning, 1974; Taylor & Cohen, 1985; Nall & Feldman, 1998). Ergometrine has also been implicated in maternal death from cardiac arrest (DHSS, 1975) and intracerebral haemorrhage (Ringrose, 1962).

McDonald *et al.* (1993) reported that the disadvantages of routine syntometrine use in the third stage of labour outweighed its advantages. They compared the use of intramuscular syntocinon with syntometrine as part of active management of the third stage of labour, in a large double-blind randomised controlled trial. Women were randomly allocated to receive either intramuscular syntocinon (n = 1753) or syntometrine (n = 1730). Similar PPH rates were reported in both study arms; whether defined as ≥ 500 mL (OR = 0.90, 95% CI of 0.75 to 1.07) or ≥ 1000 mL (OR = 0.82, 95% CI of 0.59 to 1.14). However, syntometrine was associated with a higher incidence of side effects such as nausea, vomiting, and increased blood pressure.

When compared to syntocinon, syntometrine increases the incidence of hypertension (diastolic blood pressure of > 100 mm.Hg) by a factor of five (McDonald *et al.*, 1993), and is therefore contraindicated in women with high blood pressure in pregnancy. Consequently, its routine use requires prior knowledge of the patient's blood pressure status, which is not always the case

in many parts of the world. Accidental administration of syntometrine rather than syntocinon to women with pre-existing pre-eclampsia has been reported as a precipitating factor in postpartum eclampsia. The advantages of Syntometrine must therefore be considered together its rare but serious hypertensive side effects, and its gastrointestinal side effects in the form of nausea and vomiting, which markedly reduce its acceptability.

Another disadvantage that hinders the use of Syntometrine worldwide is its storage requirements. Syntometrine should be stored between 2 to 8°C, and protected from light (Data sheet compendium, 1993). Simulation studies on different brands of ergometrine have shown that 90% of its activity is lost after one year of storage at a temperature of 21°C, which often occurs in tropical climates (Hogerzeil *et al.*, 1993). The storage requirements of syntometrine and ergometrine represent an important obstacle to the routine use of oxytocics in the developing world. Because of this, the WHO has considered the feasibility of synthesising forms of drugs that are able to withstand high temperatures, for some time, without success so far. Finally, the use of syntometrine is an invasive procedure, which is an important disadvantage in view of the rising incidence of infection over the world.

In developing countries, these and other factors are important to consider, especially in rural areas where access to a skilled birth attendant who is able to give an injection may not be possible, and/or refrigeration of drugs may be inadequate. Also, in case of an emergency, it may be more difficult to transfer a patient to a clinic or hospital. The high incidence of pregnancy anaemia and the inadequacy of blood transfusion services make it more vital to prevent avoidable loss of blood. Furthermore, it is of utmost importance to minimise blood transfusion, which is a major risk factor for transmission of HIV infection in many developing countries.

1.1.3. Role of prostaglandin agents in the management of the third stage of labour

Prostaglandins possess strong uterotonic features and play a major role in the third stage of labour. $PGF_{2\alpha}$ and its analogue 15 methyl $PGF_{2\alpha}$ (Carboprost) are potent uterine stimulants. The use of prostaglandins in the third stage of labour has been applied in two main venues; prophylactically against PPH (Kerekes & Domokos, 1979; Poeschmann *et al.*, 1991; Abdel-Aleem *et al.*, 1993; Chua *et al.*, 1995); and curatively in the treatment of intractable PPH (Corson & Bolognese, 1977; Toppozada *et al.*, 1981). The activity of prostaglandins in arresting PPH derives from their contractile action on the myometrium, which results in compression of blood supply to the placental bed. Carboprost is the drug of choice, and is universally used for the management of PPH due to uterine atony (Toppozada *et al.*, 1981; Hayashi *et al.*, 1984; Buttino & Garite, 1986; Anjaneyulu *et al.*, 1988).

Interest in the role of prostaglandins in the prophylaxis against PPH started in the seventies. Kerekes and Domokos (1979) compared intramyometrially injected $PGF_{2\alpha}$ and intravenous ergometrin with no treatment for third stage management in 140 patients. $PGF_{2\alpha}$ significantly reduced the duration of the third stage of labour, blood loss, and the incidence of subinvolution.

Poeschmann *et al.* (1991) reported that prophylactic administration of oxytocin or sulprostone directly after delivery reduces postpartum blood loss and shortens the third stage of labour. The effect of administration of Syntocinon or sulprostone was compared with physiological management, on postpartum blood loss in low risk women by means of a randomised, placebo-controlled, double-blind trial. Women received either 5 IU of oxytocin, 500 μgm of sulprostone, or 0.9% saline intramuscularly immediately after

delivery. Postpartum blood loss was reduced almost equally by about 35%, whether by oxytocin (p-value = 0.02), or sulprostone (p-value = 0.05). The mean length of the third stage was shorter in both groups receiving the active treatment, and was significant among women receiving sulprostone (p-value = 0.01).

Abdel-Aleem *et al.* (1993) used Carboprost trometamol for management of the third stage of labour, and reported that it was more potent than methyl ergometrine. It was associated with a significantly shorter duration of the third stage and significantly lower mean postpartum blood loss.

Intramuscular prostaglandins were found to be comparable to syntometrine when used for active management of the third stage of labour. Chua *et al.* (1995) conducted a randomised controlled study on 112 women with singleton pregnancies at term. Patients were randomised to receive either 0.5 mg of syntometrine or 125 μgm of prostaglandin 15-methyl $F_{2\alpha}$ (Carboprost) intramuscularly at delivery of the anterior shoulder. Prostaglandin 15-methyl $F_{2\alpha}$ (Carboprost) was reported to be similar to syntometrine in reducing the length of the third stage, incidence of PPH and total blood loss in the first 2 hours and subsequent 22 hours after delivery. However, Carboprost had the disadvantage of being more expensive, and was associated with a statistically significant increase in the incidence of profuse and frequent diarrhoea.

Despite lack of randomised trials, prostaglandin agents are recognised to be superior to oxytocics in the treatment of severe PPH. Laajoki and Kivikoski (1986) used Sulprostone (a PGE_2 analogue) to control atonic PPH in 74 women who had normal pregnancies and deliveries. Women were divided into three groups; the first received either 50 or 100 μgm of Sulprostone IV, the second received 200 μgm IM, and the third (control) received 0.2 mg

methylergometrine IM and 5 IU oxytocin IV, respectively. Blood loss was measured during the third stage of labour, and the following two hours. The pilot dose of 50 μgm was not effective enough. Blood loss in the group receiving 100 μgm IV was 386 (± 175) mL, compared to 325 (± 197) mL in the 200 μgm IM group, and 302 (± 202) mL in the methylergometrine + oxytocin group. The 200 μgm dosage of sulprostone administered intramuscularly immediately after delivery was reported to be effective in controlling atonic PPH, with mild side effects.

The efficacy of Sulprostone in the treatment of severe atonic PPH unresponsive to conventional therapy, was also demonstrated by Phuapradit *et al.* (1993), where PPH was successfully controlled in 83% of cases with blood loss >1500 mL, with tolerable side effects.

Unlike syntometrine, prostaglandins are not hypertensive, and by virtue of their strong uterotonic features and their apparent superiority in the management of PPH, they appear to be ideal agents for prophylactic use in the third stage of labour. However, most studies in the literature that have investigated the use of prostaglandins in third stage management included less than 300 patients, and extensive literature search revealed that none have investigated the use of an oral agent.

1.2. POSTPARTUM HAEMORRHAGE

1.2.1. Definition

Postpartum haemorrhage (PPH) is excessive bleeding following delivery. It is defined by the World Health Organisation (WHO) as a postpartum blood loss in excess of 500 mL in case of vaginal deliveries. PPH is a clinical diagnosis that encompasses excessive blood loss after delivery of the infant from a variety of sites; uterus, cervix, vagina, or perineum, and this may occur before, during or after delivery of the placenta. Blood loss during the first 24 hours of delivery is known as early or primary PPH. Blood loss between 24 hours up to six weeks after delivery is known as late or secondary PPH.

The minimum amount of blood loss used to diagnose PPH has varied by various authors; from 300 mL (Ratnam & Rauff, 1989) to 800 mL (Nordstrom *et al.*, 1997). A postpartum blood loss of 500 mL or more, although an arbitrary choice, is the generally accepted quantity used to diagnose PPH (Samil, 1992), since most mothers can tolerate up to this amount without risk. However, in developing countries where severe malnutrition and maternal anaemia are common, a blood loss of as little as 250 mL may be fatal (Lawson, 1967). The clinical consequences of PPH therefore depend on both maternal health and the amount and rate of haemorrhage.

Some authors have reported that, since it is usually visually determined, the amount of postpartum blood loss may be underestimated (Gilbert *et al.*, 1987). This accounts for the wide range of PPH rates quoted in the literature, which varies from 2 to 11% (Hall *et al.*, 1985, Gilbert *et al.*, 1987). When the amount of blood loss was quantitatively measured, the reported incidence of PPH rose to 20% (Brant, 1967).

Excessive postpartum bleeding causes severe postpartum hypotension which, if not quickly treated by transfusion of blood, may lead to considerable morbidity. It may lead to partial or total necrosis of the anterior pituitary gland, causing postpartum pan-hypopituitarism or Sheehan's syndrome. Acute renal failure and other organ system injury may also result, such as pancreatitis, and adult respiratory distress syndrome. Furthermore, hysterectomy may be required to control intractable haemorrhage.

1.2.2. Aetiology

Postpartum haemorrhage results from several causes that include uterine atony, genital traumatic lacerations, retained placental tissue, and coagulation defects. Physiological control of postpartum bleeding occurs by contraction and retraction of interlacing myometrial fibres which compresses the spiral arteries and veins supplying the placental bed, thus obliterating their lumens. Uterine atony occurs when the relaxed myometrium cannot contract to constrict these blood vessels, thereby causing haemorrhage. In this case, bleeding may be either brisk or slow, is usually intermittent, and is associated with uterine relaxation. Uterine atony is the most common cause of primary PPH, accounting for 80% of cases (Prendiville & Elbourne, 1989). It is usually treated by uterine massage and oxytocic agents to stimulate myometrial contractions.

The main predisposing factors to uterine atony include dysfunctional, rapid or prolonged labour, followed by operative vaginal or abdominal delivery, and excessive manipulation of the uterus (Gilbert *et al.*, 1987). Uterine overdistention due to multiple pregnancy or polyhydramnios (Stones *et al.*, 1993), delivery following antepartum haemorrhage (APH), large infant, severe

pre-eclampsia, amniotomy, and oxytocin induction or augmentation of labour (Gilbert *et al.*, 1987), all predispose to atonic PPH. Maternal risk factors include grandmultiparity, uterine fibroids, previous history of PPH, vaginal delivery after a previous caesarean section, poor nutritional status, anaemia, uterine abnormalities or infection. Epidural analgesia and general anaesthesia, particularly by halogenated compounds, especially beta-mimetic drugs (Anderson *et al.*, 1974), also predispose to atonic PPH.

The second major cause of PPH is traumatic, which comprises about 20% of all primary PPH. This constitutes "obstetric" lacerations of the female genital tract, in addition to episiotomies. Persistent bright red bleeding in spite of an apparently firm well-contracted uterus suggests a traumatic source of bleeding. Lacerations may involve the uterus, cervix, vagina, vulva, or perineum, and may occur as a result of difficult vaginal and operative deliveries, or uncontrolled delivery of a large infant. In case of episiotomies and perineal tears, excessive bleeding may occur if the cut is large, if it involves arteries or large varicosities, if it is extended and/or difficult to repair, or if there is a delay between delivery and repair.

Another cause for PPH is spontaneous rupture of the uterus, which is rare, but may occur as a result of grand multiparity, malpresentation, previous uterine surgery, and oxytocin induction of labour. Uterine rupture or rupture of a previous caesarean section scar after vaginal delivery are important causes of PPH, since bleeding may remain entirely concealed within the abdomen. Laceration of blood vessels beneath either the vaginal or vulvar epithelium can result in haematoma formation, which is also a common cause of concealed primary PPH. This is particularly dangerous as it may go unrecognized for a long time period, or until the patient goes into shock.

Retained placental tissue and membranes cause 5 to 10% of PPH, and is associated with a fivefold increase in the incidence of PPH (Fliegner & Hibbard, 1966). Adherent placental tissue or large blood clots prevent effective contraction and retraction of the myometrium, thereby impairing haemostasis at the placental site and subsequent haemorrhage. This may occur in case of placenta accreta, in manual removal of the placenta, and in unrecognised succenturiate lobe. Mismanagement of the third stage of labour by pulling on the cord with an uncontracted uterus leads to partial separation of the placenta and haemorrhage.

Retention of the placenta may occur in three different forms. Firstly, if the placenta completely separates from the uterine wall, but is then retained by constriction of the lower uterine segment or closure of the cervix, or is lying in the lower birth canal, the uterus is usually well-contracted and there is rarely significant haemorrhage. Secondly, if the placenta is adherent to the uterine tissue; which may be true or partial. True morbid adherence of the placenta (placenta accreta) is very rare, occurring in 1 in 4000 deliveries, in which case not much bleeding occurs, but there are several intermediate conditions that contribute to placental retention and haemorrhage. Partial morbid adherence of the placenta is likely to occur in the region of old caesarean or myomectomy scars, in which case haemorrhage is invariable and is often severe. Thirdly, partial separation of the placenta, which is more common, and may cause severe haemorrhage. This may occur due to a combination of factors, such as poor uterine action, especially with operative deliveries and general anaesthesia, and ineffective manipulation of the uterus after delivery of the infant. A history of PPH and/or retained placenta increases the relative risks of PPH and/or retained placenta in a subsequent birth by two to four times. This risk increases if the subsequent birth is induced, or if there had been an intervening abortion (Hall *et al.*, 1985).

Coagulation defects are also known to cause PPH. Coagulopathies in pregnancy may occur in association with abruptio placentae, excessive thromboplastin from a retained dead fetus, amniotic fluid embolism, severe preeclampsia, eclampsia and sepsis. Coagulopathies may present as hypofibrinogenaemia, thrombocytopenia, and disseminated intravascular coagulation. However, if the myometrium at or adjacent to the placental site contracts and retracts vigorously, hemorrhage is unlikely even if the coagulation mechanisms are impaired. On the other hand fatal PPH can occur from a hypotonic uterus even though the maternal blood coagulation mechanisms are normal.

1.2.3. Maternal mortality

Postpartum haemorrhage is a major cause of morbidity and mortality during childbirth in both developing (Kwast, 1991; Spies *et al.*, 1995; Ravindran & Mathews, 1996) and industrialised countries (Berg e*t al.*, 1996). At the turn of this century, PPH was the most common cause of maternal death. Up to the present day, it is still implicated as the leading cause of one-sixth of maternal deaths worldwide, and is the most common reason for blood transfusions after delivery. However, the introduction of oxytocic preparations for the prevention of PPH has contributed to a marked decline in maternal mortality (Moir, 1955).

The incidence of PPH ranges between 5 to 8% in places where active management of the third stage of labour is practised, and may be as high as 18% in places where the third stage is managed physiologically. In the United Kingdom the incidence of PPH has fallen dramatically in the last forty years. The Confidential Inquiry into maternal deaths reveal that death rates due to

PPH in the early fifties (1952 - 1954) was 107.2 per million, falling to 11.7 per million in the early seventies (1970 - 1972). With the introduction of oxytocic drugs for third stage management in the early eighties (1979 - 1981), maternal death rates due to PPH further declined to 7.3 per million (DHSS, 1986; 1996).

In spite of the introduction of active management of the third stage of labour and prophylactic use of oxytocics, which have greatly reduced maternal mortality, from one in 3,000 births in 1930 to one in 20,000 births in 1950 (Greenhill, 1951), PPH still remains an important cause of maternal deaths. Nowadays there are approximately 5 deaths per year from haemorrhage, representing 6.4 deaths/million maternities (DHSS, 1996).

In developing countries, PPH remains one of the leading causes of maternal mortality, and maternal morbidity as a result of PPH is fifty times higher than in industrialised countries (WHO, 1989; 1991). In a community based study in Zimbabwe, PPH was found to be the leading cause of maternal death in rural (40 per 100,000) but not urban (8 per 100,000) women (Fawcus *et al.*, 1995). The researchers attributed this difference to the use of prophylactic oxytocics in more developed locations. In 1991, the reported maternal death rate due to haemorrhage in the USA was 10 deaths per 100,000 live births. In developing countries, reported maternal death rates (deaths per 100,000 live births) were as follows: 22 in Bangladesh, 18 in India, 18 in Tanzania, 17 in Zambia, and 6 in Ethiopia (World Watch Paper 102, 1991). In Egypt, for example, the maternal mortality rate among women in reproductive age groups (15-49 yrs.) is estimated to be at least 22 maternal deaths per 100,000, the major cause of which is PPH (31%), followed by hypertensive diseases of pregnancy, such as toxemia and eclampsia (28%) (Kane *et al.*, 1992).

1.2.4. Methods of assessment of postpartum blood loss

In the United Kingdom, recording of the amount of blood loss immediately after delivery is a pre-requisite prior to completion of the birth register. Blood loss is usually estimated clinically by the attendant midwife or obstetrician. The adoption of the practice of routinely estimating blood loss at delivery has been an important development in improving the quality of care for pregnant women. Irrespective of the method used, the mere practice of regular estimation of postpartum blood loss helps to focus the attention of health carers on the consequences and dangers of PPH. Whilst it is true that any particular method of assessing blood loss may suffer from inaccuracies, yet its routine use by all staff in an institute will eventually lead, by nature, to some rough consistency.

Assessment of the amount of blood loss after delivery is crucial, since it serves as a guide both to the identification of the cause of bleeding, and to the correct treatment strategy and need for blood transfusion. Underestimation of blood loss and inadequate replacement of blood are main factors that contribute to maternal death following PPH (DHSS, 1982; 1986). Overestimation of blood loss can also be detrimental, since over-transfusion of blood may also lead to serious morbidity and mortality. Accurate estimation of blood loss is also fundamental for evaluation of new oxytocic drugs.

Consistency in the method of measurement of blood loss at delivery is, therefore, a very important issue. Discrepancies among the different rates of PPH reported by different hospitals are mainly due to the different methods used to estimate blood loss, which explains the discrepancy in blood loss volume reported between "quantitative measurement" and "clinical or visual" estimation.

Visual estimation is the most widely used method in the U.K and former Commonwealth countries to assess postpartum blood loss. However, most studies investigating blood loss at delivery have shown an underestimation with visual methods (estimated blood loss). When visual estimations were compared with quantitative measurements, errors of up to 45% were reported (Newton *et al.*, 1961). Brant (1967) reported a 20% rate of blood loss of > 500 mL using quantitative methods, and observed that a considerable underestimation of blood loss occurred with visual estimation even in centers with high health care standards.

Razvi *et al.* (1996) compared the accuracy of visual estimation of blood loss (EBL) with measured blood loss (MBL) at delivery and demonstrated inaccuracies with visual estimation. The higher the measured blood loss, the greater was the difference between measured and estimated blood loss. Primary PPH went undetected in some cases when blood loss was estimated visually, unless there were clear clinical signs of haemodynamic instability. They proposed that the traditional teaching that normal blood loss at delivery usually ranges between 200 to 300 mL was likely to influence visual assessment.

It is a known fact that during delivery, blood may be diluted by amniotic fluid, and some blood may be spattered on sheets and on the gowns of attendants, which gives a constant error of about 10% (Wilcox *et al.*, 1959). Furthermore, the placenta is known to carry some maternal blood in its interstitial spaces, amounting to approximately 10% of its weight.

Having highlighted the value of routine estimation of blood loss, the following section will focus on the weaknesses of the different methods used to assess

blood loss. Either clinical, haematological, or quantitative measurement methods have been used to estimate blood loss in the third stage of labour.

1. Clinical Estimation of blood loss:

Clinical examination of the haemorrhaging patient and parameters such as changes in blood pressure and pulse rate have invariably been used to assess and diagnose blood loss. Acute hypotension consequent to hemorrhage most often indicates abrupt and life-threatening blood loss. However, these parameters may be unreliable in certain circumstances. A normal healthy individual may suffer no fall in blood pressure despite an acute loss of up to 25% of total blood volume, which could be fatal if unrecognised and untreated (Hardaway, 1979). Table 1.3 demonstrates clinical symptoms and signs of blood loss. Tachycardia develops when blood loss reaches 10-15% of the blood volume, and hypotension is only observed when 15% of the blood volume is lost, which is considerably high for a parturient woman with an expanded blood volume. Although the physiologic changes of pregnancy are designed to protect the mother from bleeding at parturition, if this protective reserve is exceeded, hypovolemic shock occurs. Reliance on clinical parameters alone is therefore insufficient to alert the physician to a postpartum blood loss of 500 mL or more.

Table 1.3. Clinical symptoms and signs of blood loss

Blood loss (% of blood volume)	Arterial BP (systolic; mm.Hg)	Symptoms and signs
10 – 15	Normal	Postural hypotension, mild tachycardia
15 – 30	Slight fall	Tachycardia, thirst, weakness
30 – 40	60 – 80	Pallor, oliguria, confusion, restlessness
> 40	40 - 60	Anuria, air hunger, coma, death

Source : Ratnam & Rauf (1989)

2. Haematological estimation of blood loss:

Haematological indices commonly used in obstetric practice include white and red cell counts, haemoglobin concentration, haematocrit, mean cell volume, and mean cell haemoglobin concentration. Taylor and Lind (1981) demonstrated a marked leucocytosis during the first few days of the puerperium, falling to predelivery values at six weeks and six months postpartum. Red cell counts, haemoglobin concentration, and haematocrit tended to increase on the first postpartum day, then fell within the next few days, returning to non-pregnant values by six months. The levels of these three indices in particular were associated with whether intravenous fluids were administered during delivery, such that their values significantly decreased with IV fluid administration.

De Leeuw *et al.* (1968), used changes in red cell counts to demonstrate that blood loss at normal delivery and the following 24 hours was approximately 600 mL. This was confirmed by Pritchard *et al.* (1962) who also used red cell counts in a similar method, and demonstrated that clinically estimated blood loss was often half of the actual loss. De Leeuw *et al.* (1968) compared the decrease in red cell mass at delivery with external loss of red blood cells, among 16 women in labour. Blood was obtained 4 - 6 hrs. before delivery, and 22-24 hrs. after delivery. Red cell volume was determined using Cromium-51 tagging of red blood cells. External red cell loss averaged 98.9% of the decrease in red cell mass. External blood loss ranged from 60 to 449 mL (average 225 mL), or 4 to 28.8% of the antepartum red cell mass (average 13.7%). Primiparas lost an average of 289 mL or 18% of their red cell mass, and multiparas lost an average of 141 mL or 7.1% of their red cell mass, and this difference was statistically significant.

Ueland (1976) used haematocrit measurement for assessment of postpartum blood loss, and reported that blood loss after delivery may be related to the fall in haematocrit 24 hours later. Athavale *et al.* (1991) used haemoglobin and haematocrit to assess blood loss whilst evaluating the efficacy of intra-umbilical oxytocin versus methylergometrine or saline during the third stage of labour. The drop in haemoglobin and haematocrit was comparable among patients receiving intra-umbilical oxytocin and those managed with methylergometrine.

In a study comparing active and physiological management of the third stage of labour, Thilaganathan *et al.* (1993) estimated blood loss at delivery both subjectively and objectively among 193 women undergoing spontaneous vaginal delivery at term. Objective measurement of blood loss was carried out by comparing maternal haemoglobin in labour with that obtained on the third postpartum day. There was no significant difference in the estimated blood loss or haemoglobin drop between the two study groups (p-value > 0.5).

Nicol *et al.* (1997) argued that routine postpartum haematocrits were a valuable haematological index only among women with an EBL of over 500 mL. They conducted a case-control study aiming to identify risk factors associated with low postpartum haematocrits (below 27%) in non-anaemic patients after vaginal delivery. Identified risk factors included placenta praevia, abruption, prolonged third stage, preeclampsia, previous PPH, and previous caesarean section. The most significant risk factor was blood loss > 500 mL (OR = 4.5, 95% CI of 3.8 - 5.4).

However, haematological indices may prove to be unreliable in certain circumstances. In a retrospective survey of MBL and EBL among 200 consecutive normal and assisted vaginal deliveries (Mola, 1983), the average

reported blood loss amounted to 720 mL. However, analysis of perinatal drops in maternal haemoglobin revealed a very poor correlation between the magnitude of the drop in haemoglobin and the volume of blood lost. It can also be argued, that it is inappropriate to label any single haemoglobin or haematocrit value as being adequate or acceptable, since "adequate" values differ from patient to patient, and sometimes also vary between different stages in an individual. Furthermore, although a fall in haemoglobin or haematocrit below 10 g/dL or 30%, respectively, to 8 g/dL or 25%, may be tolerated by some patients, it is not clinically acceptable (Lundsgaard-Hansen, 1992).

3. Quantitative or measurement methods:

Four main methods of quantitative measurement of blood loss have been described (Wilcox *et al.*, 1959). They are summarised as follows:

a. Direct collection of blood in pans, with or without shunting of other fluids into separate containers,
b. Determination of changes in blood volume before and after delivery,
c. Gravimetric methods by which sponges, gauze and perineal pads are weighed before and after use. The increase in weight of all pads and fabrics used is compared to their weights before use (dry weights). One hundred gram increase in weight is converted to 100 mL of blood. This method combines both practicality and accuracy.
d. Spectrophotometric methods by which blood and sponges, gauze, or pads containing blood are mixed in a solution that converts haemoglobin to acid haematin or cyanmethaemoglobin, which in turn can be measured in a colorimeter. This is the most reliable and accurate method for measurement of small quantities of blood loss, but is not very useful in a large clinical trial since it constrains the number of participants.

Newton *et al.* (1961) reported the use of the acid-haematin method (spectrophotometric) to measure blood loss at delivery. This method involves the collection of liquid material, pads and sponges containing blood in a solution of 0.1 N hydrochloric acid, which converts the haemoglobin into acid haematin. Appropriately diluted samples of this fluid and of a sample of the patient's blood, drawn at the same time, are then read in a Klett-Summerson colorimeter. Blood loss can then be calculated by a simple formula.

Bloomfield *et al.* (1990) measured blood loss at delivery by collecting and washing all swabs, linen and blood clots in 40 mL of cold water. A dilute solution of oxyhaemoglobin prepared from 4 mL of the subject's blood diluted in 40 mL of cold water was produced for calorimetric comparison, after which blood loss was calculated by a simple formula. The value of the MBL was compared with that of the EBL, and an underestimation of 25% was observed with the visual method. This discrepancy was found to increase with the volume of blood lost.

Duthie *et al.* (1991) measured blood loss during normal delivery in 37 primiparas and 25 multiparas. A peripheral venous blood sample was collected from each patient after the onset of labour, and serum haemoglobin level was measured using the cyanmethaemoglobin method. During delivery, the patients were draped with sterile white linen, and after delivery, all the blood stained linen, pads and blood clots were collected together and placed in a cryovac plastic bag for blending. On the second day of delivery, another blood sample was obtained, and the serum haemoglobin level measured. The total amount of blood lost in the stained linen and pads was then calculated using a simple formula. Blood loss was also visually estimated at delivery. The volume of MBL was significantly greater than the EBL in both primigravid and multiparous women (p-value < 0.05). In primigravidaes, the mean EBL

was 260 mL (standard error of mean SEM ± 12) and the mean MBL was 401 mL (± 29). In multiparas the mean EBL was 220 mL (± 10) and the mean MBL was 319 mL (± 41). The discrepancy between MBL and EBL was reported to be proportional to the amount of postpartum blood loss.

Although laboratory assessment techniques used to quantify postpartum blood loss provide highly reliable and accurate results, they are also time-consuming, cumbersome, and increase the cost and duration of clinical studies. Most of the prominent studies in the literature investigating the management of the third stage of labour (Prendiville *et al.*, 1988; McDonald *et al.*, 1993; Mitchell & Elbourne, 1993; Khan *et al.*, 1995; Dumoulin JG, 1981; Nieminen & Jarvinen, 1963; Yuen, 1995; Begley, 1990), have employed the "visual or clinical" method of blood loss estimation. Since this assessment is subjective, however, other substitute indices are usually recorded, such as the change in haemoglobin concentration and haematocrit, the need for blood transfusion, the length of the third stage, and the need for therapeutic oxytocics or manual removal of the placenta.

1.3. PROSTAGLANDINS IN OBSTETRICS

The discovery of prostaglandins is associated with the name of the Swedish physiologist Von Euler. In the mid-1930's, Von Euler (1935; 1936) demonstrated a new smooth muscle stimulant in human seminal fluid and named it prostaglandin, presuming it to be a product of the prostate gland. After a gap of several years, Bergstrom *et al.* (1949) confirmed that the biological activity of human seminal fluid extract was due to a new group of highly active, lipid-soluble, unsaturated, hydroxy fatty acids. Bergstrom and Sjovall (1957) isolated the first two prostaglandins, PGE_1 and $PGF_{1\alpha}$, from sheep vesicular glands in pure crystalline form. Following that, prostaglandins were bio-synthesised from arachidonic acid, and incubates of sheep seminal vesicles in 1964, thereby making pure prostaglandin first available for study. Bergstrom *et al.* (1968) isolated and chemically identified the primary prostaglandins; a series of closely related compounds now known as PGE_1, PGE_2, PGE_3, $PGF_{1\alpha}$, $PGF_{2\alpha}$, $PGF_{3\alpha}$. Chemical synthesis of prostaglandins in 1970 further paved the way for commercial manufacture.

Prostaglandins occur naturally in most tissue of the human body. They are involved in many physiological processes; the most important of which is their role in human parturition. Prostaglandins and prostaglandin analogues have been used in obstetrics for over 25 years; for induction of abortion, as cervical priming agents, for mid trimester termination of pregnancy, induction of labour, and in the treatment of intractable PPH. The spectre of therapeutic prostaglandins is currently looming over obstetric and gynaecologic practice.

1.3.1 Natural Prostaglandins

Natural prostaglandins are locally acting hormones. They are not stored in tissues, and their biosynthesis immediately precedes their release. Prostaglandins are found in almost every tissue, and therefore demonstrate a wide range of biological activities. They constitute a group of oxygenated, polyunsaturated, fatty acids consisting of 20 carbon atoms, with a 5-membered (cyclopentane) ring, and two side chains (Figure 1.1). They are named A to I depending upon the structure of the cyclopentane ring (Figure 1.2). The side chains of prostaglandins have one or more double bonds, and are further subdivided into subgroups according to the number of double bonds in the side chains. The number of double bonds is indicated by the numerical subscript, e.g. PGE_1, PGE_2, and PGE_3 (Figure 1.3). Greek subscripts are added to clarify stereochemistry e.g. $PGF_{2\alpha}$ (Figure 1.4). However, both prostacyclines (PGI_2) and thromboxanes (TXA_2) have unusual ring structures that do not adhere to this simplified nomenclature (Figure 1.2) (Salmon & Flower, 1979).

Prostaglandins are synthesised from essential unsaturated fatty acids; the most important of which is arachidonic acid. The first step in the bio-conversion of arachidonic acid to prostaglandins (PGE_2 and $PGF_{2\alpha}$), prostacyclins (PGI_2) and thromboxanes (TXA_2), is the formation of the cyclic endoperoxides; prostaglandins G and H. The enzyme responsible for the conversion of arachidonic acid to PGH_2 is known as "fatty acid cyclo-oxygenase" or "prostaglandin endoperoxide synthetase" (Figure 1.5). Non-steroidal anti-inflammatory drugs (NSAIDs) such as Aspirin or Indomethacin inhibit the action of cyclo-oxygenase and the formation of prostaglandins. The endoperoxides PGG_2 and PGH_2 are further converted non-enzymatically into PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2 (Samuelsson *et al.*, 1975; 1978). These conversions occur very rapidly in all mammalian tissues. In in-vitro systems,

once biosynthesis is initiated, it is completed within a few minutes (Hamberg *et al.*, 1971 a, b).

Natural prostaglandins are chemically unstable and are rapidly metabolised. The enzymes involved in their metabolism are present in the lungs, liver, and kidneys (Anggard *et al.*, 1971). The main and most rapid route of metabolic degradation is by oxidation of the hydroxyl group at the site of carbon 15 by a dehydrogenase enzyme (15-hydroxy-prostaglandin dehydrogenase), which gives rise to the corresponding 15 keto-prostaglandins that are biologically inactive. A further reduction of the double bond at carbon 13 leads to the formation of 15 keto- 13,14 dihydro-prostaglandins (Figure 1.6). This by-product was found to be rapidly produced following intravenous injection of primary prostaglandins in humans (Samuelsson *et al.*, 1975). Hamberg & Samuelsson (1971) reported that within 90 seconds of injecting Tritium-labelled PGE_2 intravenously, less than 5% remains as PGE_2 (estimated half-life about 15 seconds), while 50% is converted to 15 keto- 13,14 dihydro-prostaglandin (half-life about eight minutes) in the peripheral circulation. This is followed by two stages of Beta (β) oxidation of the carboxylic acid side-chain, and one of Omega (ω) oxidation of the alkyl side-chain. This leads to the formation of a dicarboxylic acid, which has lost four carbons, and this is the main urinary metabolite.

Prostaglandins exert pharmacological actions on almost every tissue. They induce changes in cervical tissue, protect the gastric mucosa through inhibition of gastric acid secretion and cytoprotection, inhibit and induce platelet aggregation, increase vascular permeability, and regulate body temperature. The most prominent action of prostaglandins is their stimulation of the smooth muscles of various tissues, causing contraction or relaxation, depending on the tissue involved. In therapeutic doses they act on the smooth muscle of the

uterus, gut, and vasculature. Unlike oxytocin, which is relatively ineffective in early pregnancy, prostaglandins are potent stimulators of the uterine myometrium in all stages of human pregnancy.

Prostaglandins play a major role in human parturition. They are present in the amniotic fluid throughout pregnancy, and their concentrations increase during labour. The levels of PGE_2, which plays an important role in physiological cervical ripening, increases in late pregnancy and during labour, while the levels of $PGF_{2\alpha}$ rise only during labour (Karim & Devlin, 1967).

One of the first clinical uses of prostaglandins was for induction of labour (Bygdeman *et al.*, 1968; Karim *et al.*, 1969). Initially PGE_2 and $PGF_{2\alpha}$ were tested, and their efficacy was confirmed. Bygdeman *et al.* (1968) used PGE_2 infusion in escalating doses to induce labour in 7 women. Karim *et al.* (1969) successfully used $PGF_{2\alpha}$ intravenous solution to induce labour in 35 women. Following that, prostaglandins were extensively used for cervical ripening, especially PGE_2, and its efficacy was established through various routes of administration, whether intra-amniotically, extra-amniotically, vaginally, or intracervically.

However, there were many disadvantages to the clinical use of natural prostaglandins, which limited their utilisation. Natural prostaglandins have a short half-life and are rapidly inactivated, which necessitates their continuous administration to obtain the desired pharmacological action. Furthermore, they are associated with a high frequency of gastrointestinal side effects such as mild to moderate diarrhoea, in addition to stimulation of uterine contractions in early pregnancy (Dajani *et al.*, 1991). Their commercial production depends on supplies of enzymes that are limited in availability. Consequently, clinical

use of natural prostaglandins became undesirable, and was entirely replaced by prostaglandin analogues.

1.3.2. Prostaglandin Analogues

Since natural prostaglandins were not effective with oral administration, were chemically unstable, had a short duration of action and a high frequency of side effects, the development of prostaglandin analogues that possess the equivalent therapeutic features has been a major scientific success. The newly developed prostaglandin analogues were resistant to inactivation while retaining their biological activity, thereby entirely replacing the use of natural prostaglandins in clinical practice.

Second generation prostaglandins are synthetic analogues in which an alkyl group is present at C15, so that oxidation does not occur. One of the first analogues to be developed for human use was 15-methyl-$PGF_{2\alpha}$ (Carboprost), which had a half-life of 8 minutes, was 10 times more potent than $PGF_{2\alpha}$ (Green *et al.*, 1981), and was suitable for other routes of administration. Its effect on uterine contractility was found to be 100 to 400 times greater than that of the natural compound, depending on the route of administration (Bundy *et al.*, 1971; Karim & Sharma, 1972).

In Europe, the use of Carboprost (15(s)-15-methyl $PGF_{2\alpha}$, Upjohn Company) was investigated for first trimester induction of abortion (WHO, Prostaglandin Task Force, 1977). Despite a high success rate, a number of problems were reported, such as the prolonged duration of treatment, relatively high rates of pyrexia, gastrointestinal side effects and drug storage difficulties, which diminished its potential for routine clinical use (Bygdeman *et al.*, 1976;

Lauersen, 1986). In a WHO multicenter study involving 500 patients requiring second trimester termination of pregnancy, 15-methyl-$PGF_{2\alpha}$ had a success rate of 85% within 30 hours of administration, but the incidence of gastrointestinal side effects were too high for routine clinical use (WHO, Prostaglandin Task Force, 1977).

Third generation prostaglandin analogues were created by the introduction of a methyl group at C16. These analogues were more resistant to oxidation of the 15 hydroxyl group, had higher in-vivo activity (Norman, 1991), and had more specific effects on the uterine rather than gastrointestinal muscle. Several of these analogues were produced and tested for their action on the uterus. Three major ones that became available for routine clinical use are Gemeprost and Meteneprost (Upjohn Company), which are both used intravaginally, and Sulprostone (Schering Nalador 500; Schering 1989), which is administered intramuscularly. It was therefore possible to administer prostaglandin analogues by different routes, in contrast to natural prostaglandins, which had to be administered intravenously.

Synthetic prostaglandins of the E series were found to have both cytoprotective and gastric antisecretory actions, which are relevant to their therapeutic usefulness in the treatment and prevention of gastrointestinal mucosal diseases. Controlled clinical studies have proved that prostaglandins are effective in the treatment of gastric and duodenal ulcers resulting from excessive ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs). Prostaglandins and prostaglandin analogues such as misoprostol were found to be effective for the prevention and treatment of the total spectrum of NSAID-induced mucosal damage and associated gastric and duodenal ulcers.

1.4. BACKGROUND ON MISOPROSTOL

Misoprostol is a potent orally and vaginally active prostaglandin E_1 analogue. It was developed by Searle pharmaceuticals in the early seventies, and was given the trade name *Cytotec*. At first, Misoprostol was marketed as an oral anti-ulcer tablet for its strong inhibitory effect on gastric acid secretion. Since then, it has become widely used, and has developed a well-known safety record in the prevention and management of peptic ulcer disease (Collins, 1990). It is thermostable, does not require special storage conditions, and is known to have a shelf half-life of several years (Searle, 1991; Kararli *et al.*, 1991; Gaud & Connors, 1992).

Misoprostol is also a potent uterotonic agent that has been successfully used, both orally and vaginally, to induce abortion among women pre-treated with Mifepristone (Aubeny & Beaulieu, 1991; El-Refaey & Templeton, 1994 a, b). Its efficacy as a cervical priming and predilating agent has been established, and its uterotonic features are also apparent when administered for induction of labour (Fletcher *et al.*, 1993; 1994).

The effects of Misoprostol on uterine contractility have been studied in early pregnancy (Norman *et al.*, 1991) and at term before induction of labour (Neto *et al.*, 1988). Intra-uterine pressure changes after oral administration of 200, 400, and 600 μgm of misoprostol was investigated by Norman *et al.* (1991) who reported that the increase in intrauterine pressure was greatest 30 minutes after drug administration, then declined gradually. The amplitude of contractions was highest with the 600 μgm dose. Neto *et al.* (1988) investigated uterine activity after administration of 200 and 400 μgm of oral misoprostol every 4 hours, and 200 μgm vaginally, in women with intrauterine

fetal death at term. They reported that initiation of uterine activity varied between 10 to 120 minutes.

1.4.1. Pharmacology and pharmacokinetics

Previous research indicated that a potent prostaglandin analogue that possessed oral activity could be produced by blocking the oxidation of the hydroxyl group at C15, with placement of either a methyl group at C15 or two methyl groups at C16 (Steric inhibition) (Robert & Magerlein, 1973).

When a derivative of PGE_1 that had a lower side-chain at C16 instead of C15 was synthesised, the resulting analogue was found to possess weak anti-secretory activity, and was almost free of the typical prostaglandin side-effects (Collins, 1990). Adding a methyl group to carbon-16 of the 16-hydroxy prostaglandin produced misoprostol (Figure 1.7). Misoprostol has a molecular weight of 382.54, an empirical formula of C22 H38 O5, and exists as an approximate 1:1 mixture of 2 diastereomers. It was almost 35 times more potent than the 16-hydroxyl compound, and its selectivity was much improved (Karim, 1987; Collins, 1990).

A solution to the problems of chemical instability was found by means of dispersion of misoprostol by 1:100 hydroxypropyl methyl cellulose, which did not alter the basic pharmacology of the drug, but resulted in a considerably more stable product than the pure chemical form. Conventional misoprostol tablets, with a shelf life of several years, could therefore be produced (Kararli *et al.*, 1991; Gaud & Connors, 1992).

The absorption of misoprostol is extremely rapid, and it is detected in the circulation within two minutes of its oral ingestion. Its peak plasma levels in the circulation is reached in less than 15 minutes (Karim, 1987), and its elimination half-life is less than 30 min. after oral administration. The absorption of misoprostol, determined by analysing total radioactivity, is extensive, as evidenced by urinary excretion of 65-73% total radioactivity following an oral dose of 17-18 Tritium-labelled misoprostol within 7 days of ingestion. Most of this excretion occurs in the first 24 hours (Karim, 1987).

Misoprostol undergoes extensive metabolism during and/or prior to its gastrointestinal absorption. Like other prostaglandins, Misoprostol is metabolised by the fatty acid oxidising system (Beta and omega oxidation) present throughout the body. It is rapidly absorbed and de-esterified to its free fatty acid during and prior to its gastrointestinal absorption. Several metabolites are formed and no unchanged drug is detected in the plasma or urine. The biologically active metabolite of misoprostol is misoprostol acid (Figure 1.8). This fast conversion makes it almost impossible to measure the plasma concentration of the parent compound.

Misoprostol acid undergoes further metabolism by conversion via β oxidation of the α chain and ω-oxidation of the β side-chain and reduction to prostaglandin F analogues (Schoenhard *et al.*, 1985). While less than 1% of misoprostol acid is excreted in the urine and none is excreted in the faeces, its metabolites are largely excreted via these routes (Karim & Nicholson, 1989). Experimental investigations show that 80% of the inactive products are excreted in the urine, while 15% are excreted in the faeces. Due to the rapid metabolism and excretion of misoprostol and its active metabolite, misoprostol acid, there is no evidence of their accumulation in the circulation, even when multiple doses are administered (Karim, 1987).

The relationship between the dose of misoprostol and its plasma levels was described by Leese & Karim (1985), who administered 200 or 400 μgm of misoprostol with 180 mL water following an overnight fast to six healthy men. Fasting was maintained for four hours after administration of the drug. Serial plasma samples were collected in the first 24 hours for radioimmunoassay of the primary metabolite, misoprostol acid. Although the mean time to reach peak levels of misoprostol acid did not differ significantly between the two dosages, the mean peak plasma concentration of the 400 μgm dose was significantly higher than the smaller dose. In a larger randomised cross-over study, 24 healthy adult subjects were given a single oral dose of 200 or 400 μgm misoprostol. Blood samples were taken at frequent intervals for up to four hours after dosing to measure misoprostol acid levels. It was reported that increasing the misoprostol dose from 200 to 400 μgm resulted in an approximately two-fold increase in the plasma levels of the metabolite, from 397 to 835 pg/mL (Karim, 1987).

Misoprostol acid is approximately 85% serum protein bound, independent of both age and concentration (Schoenhard *et al.*, 1985). Protein binding of misoprostol is unaffected by drugs, which are either extensively bound to serum albumin, or expected to be co-administered with misoprostol. Misoprostol has no clinically important pharmacokinetic interaction with Aspirin, Indomethacin, Ibuprofen, or Diclofenac (Nicholson *et al.*, 1990).

Zieman *et al.* (1997) compared the pharmacokinetics of vaginally and orally administered misoprostol among 20 women, receiving a 400 μgm dosage either orally or vaginally. Serum levels of misoprostol acid were measured in the blood at 7.5, 15, 30, 45, 60, 90, 120, and 240 minutes. The first 10 women were pregnant, and undergoing first-trimester abortions. The other ten women were not pregnant and had additional blood sampling at 360 min. The extent

of absorption of misoprostol was highly variable among patients depending on the route of administration, and was significantly higher with oral intake. The mean concentration of misoprostol acid with oral administration was significantly higher (277 ± 124 pg/mL compared to 165 ± 86 pg/mL, p-value = 0.03), and the mean time to reach peak blood levels was significantly shorter (34 ± 17 min. compared to 80 ± 27 min, p-value < 0.001). However, areas under the misoprostol serum concentration versus time curve showed a prolonged serum concentration in the vaginal group, which indicated a prolonged duration of action with vaginal administration. These significant differences in the pharmacokinetics of misoprostol may explain the differences in clinical efficacy between the vaginal and oral routes of administration. Furthermore, assuming that the pharmacologic effect of misoprostol is related to its plasma concentration, its prolonged serum concentrations among women receiving the drug vaginally suggests that vaginal administration could be dosed at longer intervals than oral.

1.4.2. Licensed applications of Misoprostol

Misoprostol is currently primarily licensed worldwide for the prevention of non-steroidal anti-inflammatory drug-associated gastric and duodenal ulcers, hundreds of publications having highlighted its use in this field. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment of rheumatic diseases. However, a significant number of patients receiving these drugs experience upper gastrointestinal side effects and injury to the gastroduodenal mucosa. This may range from clinically insignificant bleeding and minor erosive changes to deeper bleeding ulcers and perforation, which mainly occur in the stomach and less frequently in the duodenum. Endoscopic studies have found that 14-31% of long-term NSAID users have gastric or duodenal ulcers

(Miller, 1992). Gastrointestinal injury resulting from NSAIDs is associated with increased morbidity and mortality as a result of bleeding and perforation, which may lead to the premature death of 3000 to 4000 patients in the UK annually (Hayllar *et al.*, 1992).

The damaging effects of NSAIDs on the gastrointestinal tract, and the consequent occurrence of mucosal lesions is believed to occur as a result of two actions; a direct damaging effect on the integrity of the mucosa, and local depletion of endogenous mucosal prostaglandins. The immediate actions of NSAIDs operate at a subcellular level; in particular altering mitochondrial function, which causes depletion of ATP and renders the cell vulnerable to oxidant stress. This leads to inhibition of prostaglandin synthesis, which, in turn, delays cellular repair.

Prostaglandins protect the gastric mucosa by decreasing gastric acid secretion, increasing mucus and bicarbonate production and maintaining mucosal blood flow (Ballinger, 1994), particularly the E-class of prostaglandins secreted by the gastrointestinal mucosa and other organs. Animal studies have documented the concept of cytoprotection as the mechanism by which prostaglandins protect the gastric mucosa. Due to their important role in maintaining the integrity of the gastrointestinal tract, prostaglandins are therefore considered effective for prevention of NSAID-induced mucosal damage.

Misoprostol is effective in the prevention and treatment of NSAID-induced gastro-duodenal mucosal damage, and has been reported to be therapeutically superior to other agents in this respect. It has been recommended that the use of NSAIDs be accompanied by sufficient mucosal protection by co-administration of misoprostol (Bolten, 1991; Agrawal & Saggioro, 1991; Agrawal & Dajani, 1992; Ballinger *et al.*, 1992; Hawkey, 1993; Agrawal *et*

al., 1995 a, b; Agrawal, 1995 a, b; Dajani & Agrawal, 1995 a, b). Misoprostol may be the only antiulcer drug proven to be effective in the prevention of NSAID-induced gastric and duodenal ulcers, and in reducing upper gastrointestinal complications such as perforation and/or haemorrhage (Ardizzone & Bianchi-Porro, 1996).

It is thought that the protective effects of misoprostol on the gastroduodenal mucosa of NSAID-treated patients are largely mediated by mechanisms other than inhibition of acid secretion (Henriksson *et al.*, 1993). Misoprostol stimulates basal gastric mucus and bicarbonate secretion in the proximal and distal duodenum (Bauer, 1985; Isenberg *et al.*, 1986; Wilson *et al.*, 1986). This effect is dose-dependent, such that an increase in single dose administration of misoprostol from 200 to 800 μgm increases basal gastric mucus secretion from 35% to 95% (Wilson *et al.*, 1986).

The use of misoprostol is associated with a substantial improvement in the endoscopic and histologic appearance of the gastric mucosa of patients with symptomatic chronic erosive gastritis, and significantly reduces the extent of symptoms (Pazzi *et al.*, 1994). The only significant side effect to the use of misoprostol for treatment of NSAID-induced gastro-duodenal ulcers is mild and transient diarrhoea and abdominal cramps (Dajani *et al.*, 1991).

Prophylactic treatment with misoprostol is especially recommended for patients at risk of ulcer complications, such as those with previous peptic ulcer, elderly or medically compromised patients receiving large doses of NSAIDs, and those receiving additional steroids. Misoprostol has also been reported to be of equal efficacy to H_2 antagonists in the healing of ordinary gastric and duodenal ulcers not associated with NSAID use (Ballinger, 1994).

1.4.3. Other applications of Misoprostol

Recent research has suggested that the protective role misoprostol exhibits on the gastrointestinal tract may be extended to other tissues. Prostaglandins are known to be important modulators of renal physiology, and protect renal tubule epithelial cells from hypoxic injury at the cellular level (Paller & Manivel, 1992). Misoprostol demonstrates on the kidneys the same cytoprotective effect as that on the gastrointestinal epithelium, producing an increase in urinary volume and urinary sodium excretion and a decrease in urinary osmolality. A low dose of misoprostol is vasodilatory, natriuretic, and diuretic, producing a transient but significant increase in the glomerular filtration rate and effective renal plasma flow, and a decrease in renal vascular resistance. In high doses, however, it increases renal vascular tone and inhibits sodium and water excretion (Wong *et al.*, 1994). Misoprostol was found to provide significant protection against ischaemia-induced renal dysfunction in rats. Misoprostol-treated rats were reported to have glomerular filtration rates almost three times greater than controls, and improved tubular function.

In terms of its effect on blood pressure, misoprostol exerts a modest but transient antihypertensive effect. Kailasam *et al.* (1994) reported a slight decrease in mean arterial blood pressure 20 minutes after administration of 400 μgm of misoprostol orally. This was accompanied by a decrease in systemic vascular resistance and a compensatory rise in cardiac output and heart rate. However, in spite of this transient antihypertensive effect, it was thought that misoprostol was unlikely to have therapeutic benefit in essential hypertension.

Misoprostol has been shown to possess some of the allergic mediator features of E series prostaglandins, which influence both humoral and cellular immune

reactions in animals and in man (Iyengar *et al.,* 1991). In a randomised placebo-controlled trial, a dose of 800 μgm of misoprostol per day was found to induce changes in the circulating levels of IgM rheumatoid factor (Goodwin & Clay, 1987).

Animal studies have shown that misoprostol has the potential to be used as an immuno-suppresive agent. The immuno-modulatory and vasodilator activities of misoprostol have been utilised in the field of organ transplantation. When given in combination with cyclosporins, misoprostol improved the survival of cardiac transplants in animals (Weiderkeher *et al.*, 1990). Misoprostol has also been reported to improve renal function in renal transplant patients, and to decrease the incidence and number of renal transplant rejection episodes (Burgess & Muruve, 1992; Pouteil-Noble *et al.*, 1994).

The therapeutic applications of misoprostol beyond the gastrointestinal tract appear to be among the most interesting of therapeutic advances offered by any class of compound in the next decade. Misoprostol has been reported as an effective treatment for conditions that vary in severity from minor ailments, such as chronic constipation (Soffer *et al.*, 1994) or as a treatment for tinnitus (Briner *et al.*, 1993), to major conditions, such as its inhibitory effect on early tumour growth of some colonic cancers (Lawson *et al.*, 1994). Other reported therapeutic applications for misoprostol include chondroprotection, limitation of renal, hepatic, gastrointestinal and radiation-induced tissue injury, and prevention of inflammatory and allergic disorders (Shield, 1992; 1995).

1.4.4. Misoprostol in Obstetrics and Gynaecology

a. Induction of Abortion and mid-trimester termination of pregnancy

The abortifacient properties of misoprostol were first reported in Brazil, where it was used by women attempting abortion of unwanted pregnancies. Abortion in Brazil is legal only in cases of rape or incest, or to save a woman's life. Despite all other reasons being illegal, induced abortion is widely carried out. When used illegally, misoprostol may be inefficient in achieving complete abortion, and many women may suffer from incomplete abortions which may require uterine evacuation.

Doses used for illegal abortion ranged from 200 μgm up to 16,800 μgm of misoprostol. Most women took the drug orally, some used a combination of oral and vaginal routes, and few administered it intravaginally. The most common pattern of use associated with the highest abortion rate was 4 tablets of 200 μgm of misoprostol each; administered as 2 tablets orally and 2 tablets intravaginally, mainly around the ninth to twelfth week of amenorrhea (Coelho *et al.*, 1994; Fonseca *et al.*, 1996). Women sought hospital care only if complications such as severe vaginal bleeding and uterine cramps occurred (Costa & Vessey, 1993; Faundes *et al.*, 1996).

Since progesterone is essential for the establishment and maintenance of pregnancy, it has been recognised that a substance that antagonises the action of progesterone i.e. an antiprogestin, would have potential as an antifertility agent. Antiprogestin not only activates the uterus, but can also cause bleeding, uterine contractions, and ripening of the cervix. It causes an increase in uterine contractility and a significant increase in myometrial sensitivity to

prostaglandins, which is probably due to the release of the inhibitory effect of progesterone. However, antiprogestin alone is not sufficiently effective for terminating early pregnancy.

Administration of the progesterone antagonist Mifepristone (RU 486), which sensitises the uterus to prostaglandins, produces vaginal bleeding and uterine contractions in both non-pregnant and pregnant women. Extensive trials have established that a single dose of mifepristone followed 36 to 48 hours later by a prostaglandin, is an effective and safe alternative to vacuum aspiration for termination of early pregnancy. In the United Kingdom, mifepristone is used in combination with a prostaglandin agent for induction of abortion at $\leq$ 63 days gestation.

Misoprostol increases uterine activity in early pregnancy, and is associated with a significant increase in the amplitude and frequency of uterine contractions (Norman *et al.*, 1991). Several studies have proved that the combination of Misoprostol administered after mifepristone is a successful, inexpensive, simple regimen for medical termination of early pregnancy, in terms of its tolerance, safety, and minimal side-effects (Bygdeman *et al.*, 1994; Peyron *et al.*, 1993; El-Refaey & Templeton, 1994 a, b; 1995 b). The combination of methotrexate and misoprostol has been reported as the method of choice to induce abortion in women with uterine or cervical anomalies, in which case suction curettage may be difficult or impossible (Schaff *et al.*, 1996). Side effects associated with misoprostol include nausea, vomiting, diarrhoea, hypotension, fever, headache and abdominal pain (Lawrie *et al.*, 1996, Haberal *et al.*, 1996).

In a review of the literature on medical abortion in early pregnancy, Grimes (1997) reported that both mifepristone and methotrexate when used with a

prostaglandin, could safely and effectively induce early pregnancy abortion. Single, oral mifepristone doses of 200 and 600 mg had similar efficacy when used with a prostaglandin agent. Sequential and single-dose regimens had comparable efficacy. An 800 μgm dosage of misoprostol when administered vaginally as an augmenting agent, was found to be more effective than the same dose given orally (Creinin, 1996 b; Wiebe, 1996). Regimens of mifepristone or methotrexate followed by misoprostol were found to be more effective than misoprostol alone. However, the risk of haemorrhage and gastrointestinal side effects were found to be greater with medical abortion than with suction curettage.

The efficacy of misoprostol in achieving abortion, however, decreases with the duration of pregnancy; falling slightly between 49 and 56 days, and then significantly decreasing between 56 and 63 days of pregnancy (McKinley *et al.*, 1993; Aubeny *et al.*, 1995). The vaginal route of administration of misoprostol appears to be more effective and better tolerated than the oral route in induction of first-trimester abortion after pre-treatment with mifepristone. Gastrointestinal side effects, such as vomiting and diarrhoea, were also found to occur more frequently among women who receive misoprostol orally than among those who receive it vaginally (El-Refaey & Templeton, 1995 b; Schaff *et al.*, 1996; Creinin *et al.*, 1997 a, b).

Misoprostol also plays a role as a cervical priming agent in facilitating surgical abortion. Several studies have reported the success of misoprostol, whether administered orally or vaginally, in softening the cervix and facilitating cervical dilatation in women undergoing first-trimester abortion, in both nulliparous and multiparous patients (Bugalho *et al.*, 1994 a; Ngai *et al.*, 1995 a, b; Ngai *et al.*, 1996 b; Schaub *et al.*, 1996; Koopersmith & Mishell, 1996). El-Refaey *et al.* (1994 c) reported that misoprostol is comparable to gemeprost

in its leading to increased baseline cervical dilatation, reduction in the mechanical force required to dilate the cervix, and reduction of blood loss. Misoprostol was found to induce clinical and histochemical changes in the cervix similar in nature and degree to Gemeprost.

In the early nineties, the most widely used medical method of terminating second trimester pregnancy was intravaginal administration of the prostaglandin E_2 Gemeprost. This treatment was highly effective, but was associated with gastrointestinal side effects and hyperpyrexia. Since then, many studies have investigated and proved the safety and efficacy of misoprostol, administered intravaginally or intracervicovaginally, in achieving termination of pregnancy after eleven weeks of gestation (Bugalho *et al.*, 1993 b, 1996; Merrell & Koch, 1995; Del-Valle *et al.*, 1996; Wong *et al.* 1996; Srisomboon *et al.*, 1997 b).

El-Refaey *et al.* (1993) demonstrated the efficacy and acceptability of misoprostol in achieving second-trimester abortion, when compared with gemeprost, among patients pre-treated with mifepristone. There were no significant differences between the two groups in terms of the induction to abortion interval or side effects. When misoprostol was compared with Dinoprostone for second-trimester induction of abortion, side effects were reported to occur more often among women receiving dinoprostone, such as pyrexia, uterine pain, vomiting, and diarrhoea. In addition, the average cost per treatment was much higher with dinoprostone (Jain & Mishell, 1994). Bugalho *et al.* (1996) reported that vaginally administered misoprostol used in combination with methylergometrine was highly efficient in achieving complete evacuation of the uterus in second-trimester termination of pregnancy.

Misoprostol has been recommended as the prostaglandin of choice for second-trimester pregnancy termination following pre-treatment with mifepristone. The efficacy of orally administered misoprostol has also been demonstrated as a simple, inexpensive and easy procedure for second-trimester termination (Batioglu *et al.*, 1997). However, vaginally administered misoprostol was reported to be more effective than oral misoprostol in that respect (El-Refaey & Templeton, 1995 b). The median induction to abortion interval in women receiving misoprostol vaginally was found to be significantly shorter than among those receiving it orally. The median amount of misoprostol used vaginally was also significantly lower (Ho *et al.*, 1997).

b. Induction of labour

Induction of labour is indicated in postdates pregnancy, poor fetal growth, premature rupture of membranes (PROM), and maternal medical complications, such as diabetes mellitus and pregnancy-induced hypertension.

Several studies have reported that, from a clinical and perinatal perspective, misoprostol is an effective, acceptable, and safe alternative to other labour ward induction policies, and is more effective than oxytocin or PGE_2 gel. Misoprostol is an inexpensive agent that can be used to induce labour safely and effectively, while minimising the high cost associated with intravenous oxytocin infusion. Women who receive misoprostol experience a significantly reduced mean time from induction to onset of contractions, mean time to rupture of membranes, and mean time to delivery. When compared to currently used regimens in induction of labour, no difference in methods of delivery were reported, and misoprostol was associated with a significantly shorter induction to delivery interval, and its use was not associated with

higher intrapartum or neonatal complications (Fletcher *et al.*, 1993; Chuck & Huffaker, 1995; Varaklis *et al.*, 1995).

Although it has been reported that hyperstimulation, uterine polysystole (over five contractions in ten minutes) and tachysystole (six or more uterine contractions in a ten minute window for two consecutive ten minute periods) occur more frequently among women induced by misoprostol, these complications are rapidly reversible by tocolytics and do not appear to increase the risk of adverse intrapartum, perinatal, or neonatal outcomes (Srisomboon *et al.*, 1996).

Published data confirm the safety and efficacy of intravaginal misoprostol as a cervical ripening and labour-inducing agent. In a meta-analysis of published randomised trials assessing the safety and efficacy of misoprostol for cervical ripening and labour induction (Sanchez-Ramos *et al.*, 1997 c), women who received misoprostol had a significantly lower overall caesarean section rate and a higher frequency of vaginal deliveries within 24 hrs. of drug administration. Misoprostol was associated with a higher incidence of tachysystole but not hyperstimulation, but the frequencies of abnormal 5-minute Apgar scores and admissions to the neonatal intensive care unit were similar in the misoprostol and control groups. The pooled estimate of the mean interval from start of induction to delivery was 4.6 hrs. shorter in the misoprostol group.

When compared to intravenous oxytocic infusion, the induction to vaginal delivery interval is significantly shorter and delivery within 24 hrs. occurs significantly more common among women induced with misoprostol. Furthermore, misoprostol has been reported to reduce both the need for

epidural analgesia and the caesarean section rate (Sanchez-Ramos *et al.*, 1993; Bugalho *et al.*, 1995 a, b; Kramer *et al.*, 1997).

When compared to dinoprostone, misoprostol was found to be more efficient for inducing labour at term. The average induction to vaginal delivery interval is significantly shorter with misoprostol, and oxytocin augmentation of labour is required more often among women receiving dinoprostone. No significant differences in spontaneous labour rates, type of delivery, fetal outcome, or maternal complications in association with misoprostol have been reported. In spite of a reportedly higher prevalence of tachysystole in women receiving misoprostol, no significant differences were reported in the frequency of hyperstimulation or hypertonus (Chuck & Huffaker, 1995; Varaklis *et al.*, 1995; Fletcher *et al.*, 1994; Wing *et al.*, 1995 a, b; Lee, 1997).

When intravaginal misoprostol was solely used for induction of labour, the success rate was extremely high, all patients reaching the active phase of labour without oxytocin augmentation. The cervical score was significantly improved, and the interval from induction to onset of labour, and the duration of labour were both significantly short. (Bugnon *et al.*, 1994; Bugalho *et al.*, 1995 a, b, c; Wing & Paul, 1996; Srisomboon *et al.*, 1996, 1997 a; Mundle & Young 1996; Sanchez-Ramos *et al.*, 1997 a, b; Farah *et al.*, 1997).

Induction of labour using orally administered misoprostol was also successful, and was not associated with any clinically or statistically significant differences in maternal secondary outcomes, such as caesarean section rate, epidural use, perineal trauma, manual removal of the placenta, gastrointestinal side effects, or neonatal outcomes (Ngai *et al.*, 1996 a; Windrim *et al.*, 1997). However, the vaginal route of administration was associated with a higher

success rate within a shorter time interval, and using a lower dosage than the oral route (Toppozada *et al.*, 1997).

1.4.5. Safety and toxicity of misoprostol

Misorostol was internationally marketed as an oral tablet for the treatment of peptic ulcer in 1986. It is a safe and well tolerated drug when administered within the recommended dosage of 800 μgm per day. Single misoprostol doses of up to 800 μgm and total daily doses of up to 2200 μgm are well tolerated for a period of up to 3 months (Herting & Nissen, 1986; Data sheet compendium, 1993). However, the safety of higher doses is not well documented.

The safety and tolerance of a high single dose of misoprostol was investigated by Fakouhi *et al.* (1987) in a randomised double-blind parallel group study. Once daily doses of 800 μgm and 400 μgm of misoprostol administered at bed time for 14 days were compared with placebo in 37 healthy male volunteers between 18 to 55 years of age. Twenty-one subjects remained asymptomatic, and the only side effects reported were mild gastrointestinal symptoms.

Previous studies in the literature investigating the toxicity of misoprostol on animals reported no fetotoxic or teratogenic effects at doses of up to 10,000 μgm/kg body weight, but, in spite of these high doses, its uterotonic characteristics were not identified. These studies, therefore, are of no validity in humans, since almost 80% of pregnancies are interrupted by misoprostol at doses of 10 to 15 μgm/kg body weight (Bugalho, 1993 a).

Side effects associated with Misoprostol are mainly gastrointestinal, and are dose-dependent (Inman, 1991), nausea and vomiting being the most common. The Prescription Event Monitoring Survey reported a 4% rate of nausea and vomiting during the first month of treatment with misoprostol. Diarrhoea is the second most common side effect, and has been reported to occur in 10% of patients receiving 200 μgm of misoprostol four times a day. It is usually mild, and does not require any therapeutic intervention in the majority of cases.

Another major side effect to misoprostol is excessive uterine contractility with high doses. Uterine rupture has been reported as a result of excessive contractions after using intravaginal misoprostol during induction of labour at term (Bennett, 1997).

Because of its abortifacient properties, Misoprostol has been extensively misused for illegal induction of abortion. However, unsupervised use of this drug may result in incomplete abortion, which may consequently lead to bleeding or intrauterine infection. An uncertain number of abortion attempts using misoprostol are unsuccessful and, if the pregnancy continues, there may be either signs of toxicity in the mother or congenital malformations in the infant. Manifestations of toxicity or overdosage of misoprostol in the pregnant mother include hypertonic uterine contractions with fetal death, hyperthermia, tachycardia, tremors, rhabdomyolysis, hypoxemia, respiratory alkalosis, and metabolic acidosis (Graber & Meier, 1991; Bond & Van-Zee, 1994; Austin *et al.*, 1997).

The first case of misoprostol toxicity was reported by Graber & Meier (1991), in which a 71 year old woman with a history of rheumatoid arthritis and peptic ulcer, accidentally ingested 3 mg of misoprostol, almost 15 times the maximum recommended therapeutic dosage. She rapidly developed shivering

and tremors in all extremities, hyper-reflexia, a high temperature of 39.2°C, tachycardia (pulse rate = 120), hypertension (BP = 160/110), nausea, and abdominal cramps.

Bond & Van-Zee (1994) reported another case of misoprostol overdosage in a 19 year old, 31 weeks pregnant patient, who had ingested 30 tablets of 200 μgm of misoprostol and 4 tablets of 2 mg trifluoperazine (Stelazine) in a suicide attempt. Manifestations of toxicity included hypertonic uterine contraction with fetal death, hyperthermia (temperature of 41.3°C), tachycardia (heart rate = 145 beats/min.), rhabdomyolysis, hypoxemia, respiratory alkalosis, and metabolic acidosis.

Austin *et al.* (1997) reported overdosage and fetal death in a 25-year-old pregnant woman, who self-administered 6000 μgm of misoprostol intravaginally, and 600 μgm orally. She rapidly developed shivering and chills, abdominal and extremity cramping, vomiting, and confusion. Hypotension and hyperthermia (temperature of 41.4°C) developed within 3.5 hrs. of drug administration. Ultrasound showed no heartbeat and no fetal movement so the dead fetus was delivered by emergency caesarean section. The mother received supportive treatment, such as intravaginal decontamination and endotracheal intubation with neuroparalytic therapy to control agitation and hyperthermia. Recovery was complete within 15 hours of overdosage. This pyrogenic effect of misoprostol has also been reported by Baulieu *et al.* (1992) where recurrent bouts of pyrexia occurred in response to misoprostol administration in a cirrhotic patient.

With regards to the unborn infant, continuation of the pregnancy after misoprostol overdosage may result in certain congenital malformations. The vasoconstrictive and/or mechanical effects of misoprostol may explain the

occurrence of Mobius syndrome (Congenital facial paralysis) as a result of both vasoconstriction and uterine contractions at about the sixth or seventh week of pregnancy (Graf & Shepard, 1997). Congenital malformations of the scalp and cranium, cranial nerve defects, in addition to limb abnormalities were also reported among fetuses after failed first trimester abortion attempts with misoprostol (Fonseca *et al.*, 1991, 1993; Gonzalez *et al.*, 1993). Gonzalez *et al.* (1993) suggested that uterine contractions induced by misoprostol cause vascular disruption and brain stem ischaemia in the fetus.

1.5. RATIONALE OF THIS STUDY

Postpartum haemorrhage is one of the leading causes of maternal morbidity and mortality. An intervention for management of the third stage of labour aiming to decrease postpartum blood loss with minimal side effects has been sought for decades. This intervention should ideally have potential for use at both tertiary care centres in industrialised countries, and at primary care level in first line health care units in developing countries.

Current oxytocics used in the management of the third stage of labour are associated with several side effects, such as transient rise in blood pressure, headache, nausea, and vomiting. Because of its hypertensive properties, syntometrine is contraindicated in women with high blood pressure in pregnancy. In developing countries the routine use of the current oxytocic agents is not practical because of their instability at high temperatures, the invasiveness of the procedure, and the requirement of prior knowledge of patients' blood pressure status. Under these circumstances, the ideal preparation that could be used to replace the currently known oxytocics has to be effective, with minimal side effects, thermostable, orally administered and cheap.

Because of the proven uterotonic properties and known advantages of misoprostol in terms of its oral effectiveness, thermostability, low expense, and low incidence of side effects, it may be the ultimate drug of choice for the management of the third stage of labour. We aimed to investigate its role in third stage management, and to compare it with other oxytocics used in this field. If the superiority of misoprostol to other oxytocics in third stage management and the prevention of PPH could be proved, then this would have major public health implications.

This thesis describes a series of studies investigating the role of misoprostol in the management of the third stage of labour, and questions whether it is justifiable, in terms of maternal morbidity, to use orally administered misoprostol in place of the currently used parenterally administered oxytocics. The effect of different doses of oral misoprostol on uterine contractility in the third stage of labour and its associated side effects is investigated, along with its role in the emergency treatment of primary atonic PPH.

Table 1.1. Rates of postpartum haemorrhage (≥ 500 mL) in published randomised trials of third stage management

Trial-year	Intervention	Main comparison	Number	%
Daley, 1951	Oxytocin	Oxytocic vs. none	45/490	9.1
McGinty, 1956	All oxytocics	Oxytocic vs. none	1/150	0.6
Friedman, 1957	None All oxytocics	Oxytocic vs. none	24/717 2/177	3.3 1.1
Nieminen, 1963	Syntometrine Oxytocin	Syntometrine vs. oxytocin	5/689 9/689	0.7 1.3
Howard, 1964	None All oxytocics	Oxytocic vs. none	25/470 24/963	5.3 2.4
Dumoulin, 1981	Syntometrine Oxytocin	Syntometrine vs. oxytocin	52/1000 74/750	5.2 9.8
Rooney, 1985	Syntometrine None	Oxytocic vs. none	34/346 42/278	9.8 15.1
Prendiville 1988	Syntometrine None	Active vs passive management	50/846 152/849	5.9 17.9
Thornton, 1988	Oxytocin None	Oxytocic vs. none	0/10 1/15	0 6.6
McDonald 1993	Syntometrine Oxytocin	Syntometrine vs. oxytocin	247/1661 277/1672	14.8 16.5
Mitchell, 1993	Syntometrine Oxytocin	Syntometrine vs. oxytocin	6/230 17/231	2.6 7.3
Khan, 1995	Syntometrine Oxytocin	Syntometrine vs. oxytocin	27/1016 30/1012	2.7 3.0
De Groot, 1996	Oxytocin Ergometrine	Oxytocin vs. oral ergometrine	25/78 54/146	32.0 37.0

Table 1.2. Rates of postpartum haemorrhage (≥ 1000 mL) in published randomised trials of third stage management

Trial-year	Intervention	Main comparison	No.	%
Poeschmann, 1991	Sulprostone Oxytocin Saline	Oxytocin vs. Sulprostone vs. Saline	1/22 2/28 3/24	5.0 7.0 12.0
Abdel-Aleem, 1993	Carboprost Ergometrine	Carboprost vs. Ergometrine	0/73 0/77	0 0
Yuen, 1995	Syntometrine Oxytocin	Syntometrine vs. oxytocin	6/496 10/495	1.2 2.0
De Groot, 1996	Ergometrine Oxytocin Placebo	Ergometrine vs. Oxytocin vs. Placebo	12/146 7/78 16/143	8.0 9.0 11.0

Figure 1.1: Hypothetical prostanoic acid skeleton

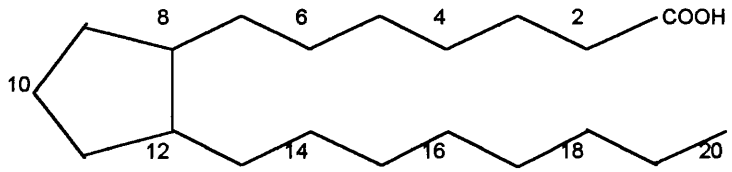


Figure 1.2: Structures of cyclopentane rings of common prostaglandins:

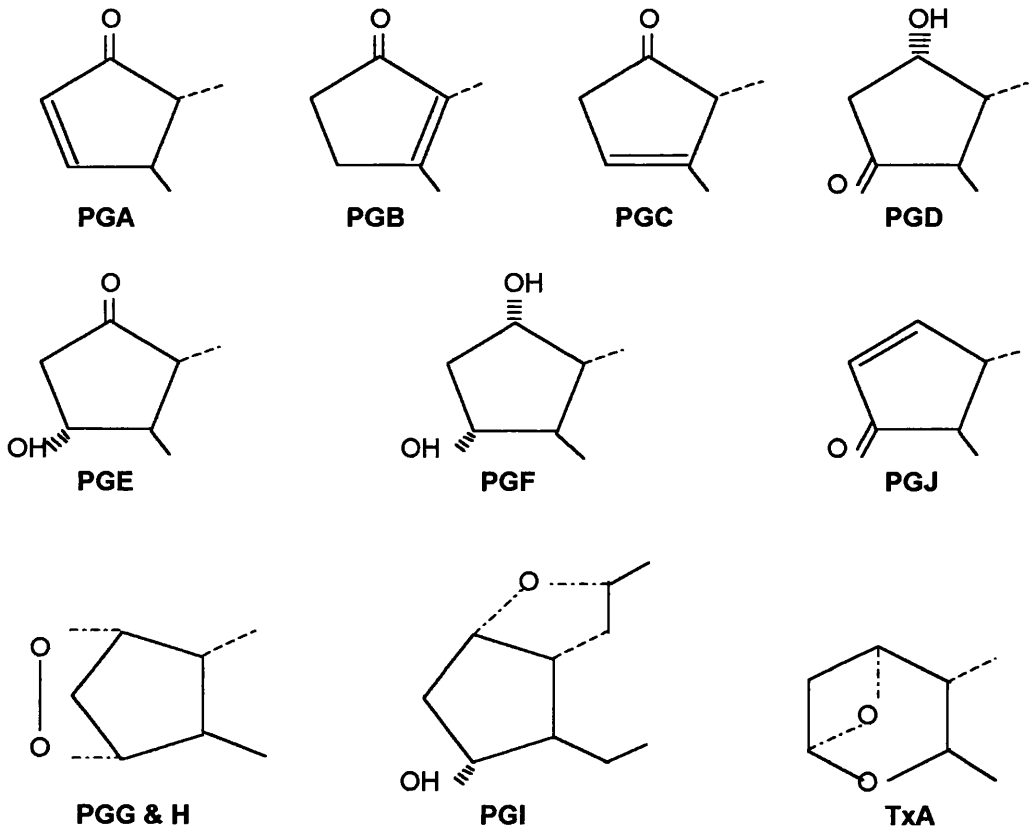


Figure 1.3. Structure of prostaglandin E_1, E_2, and E_3:

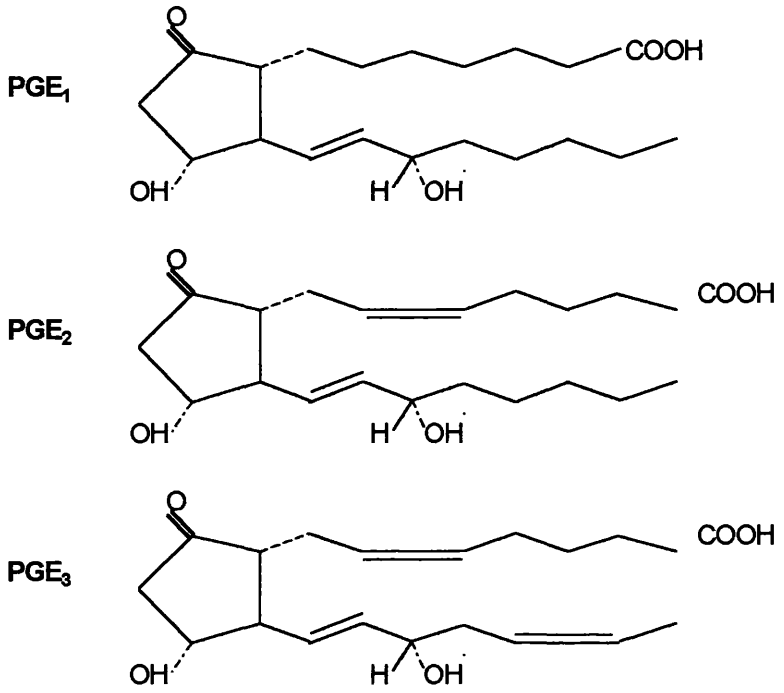


Figure 1.4. Structures of the α and β isomers of the PGF_2 :

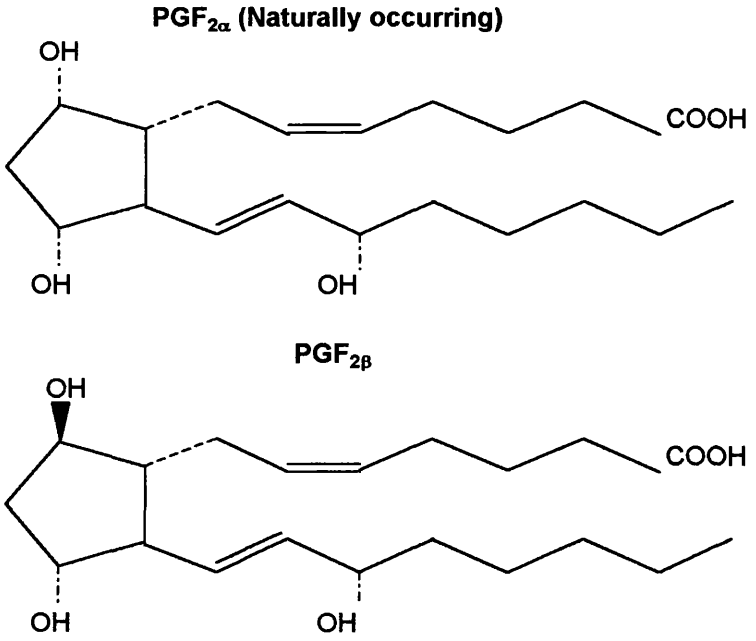


Figure 1.5: Biosynthesis of prostaglandins from Arachidonic acid

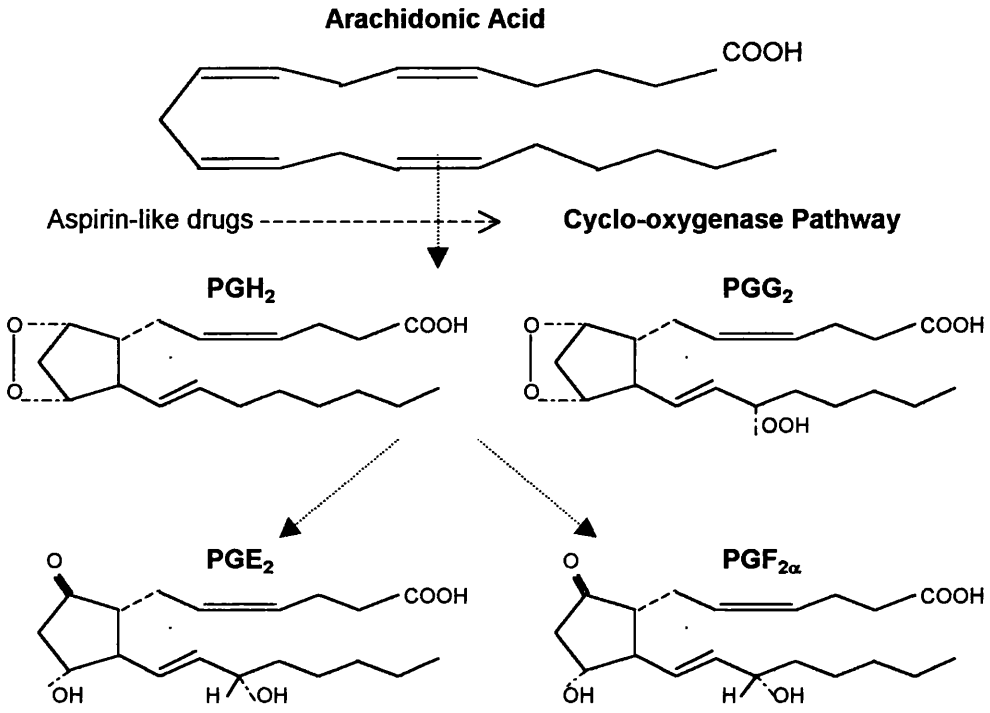


Figure 1.6: Metabolic pathway of prostaglandins

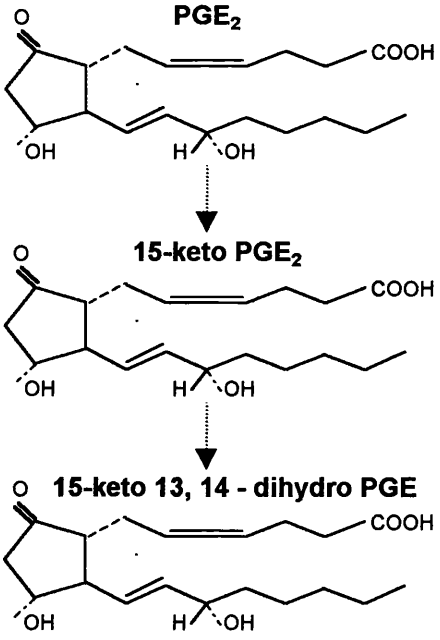


Figure 1.7. Structure of Prostaglandin E_1 analogue and the development of misoprostol:

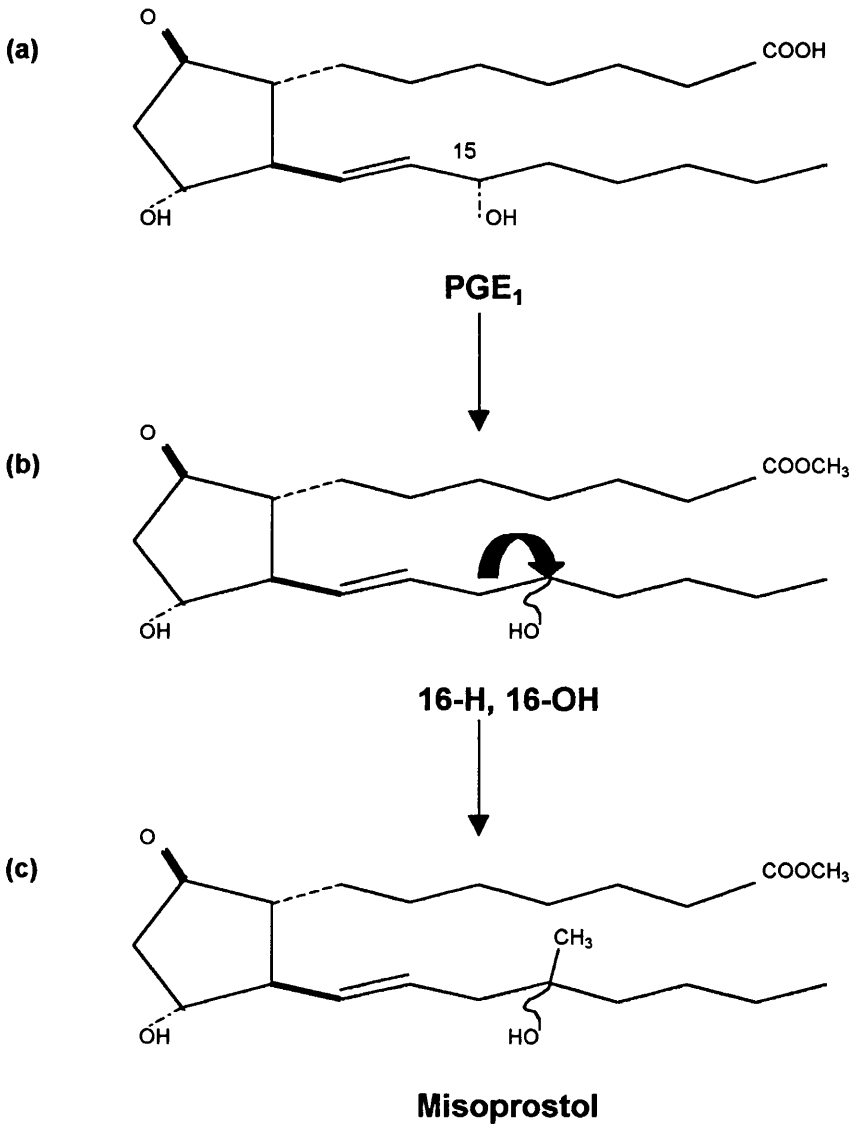
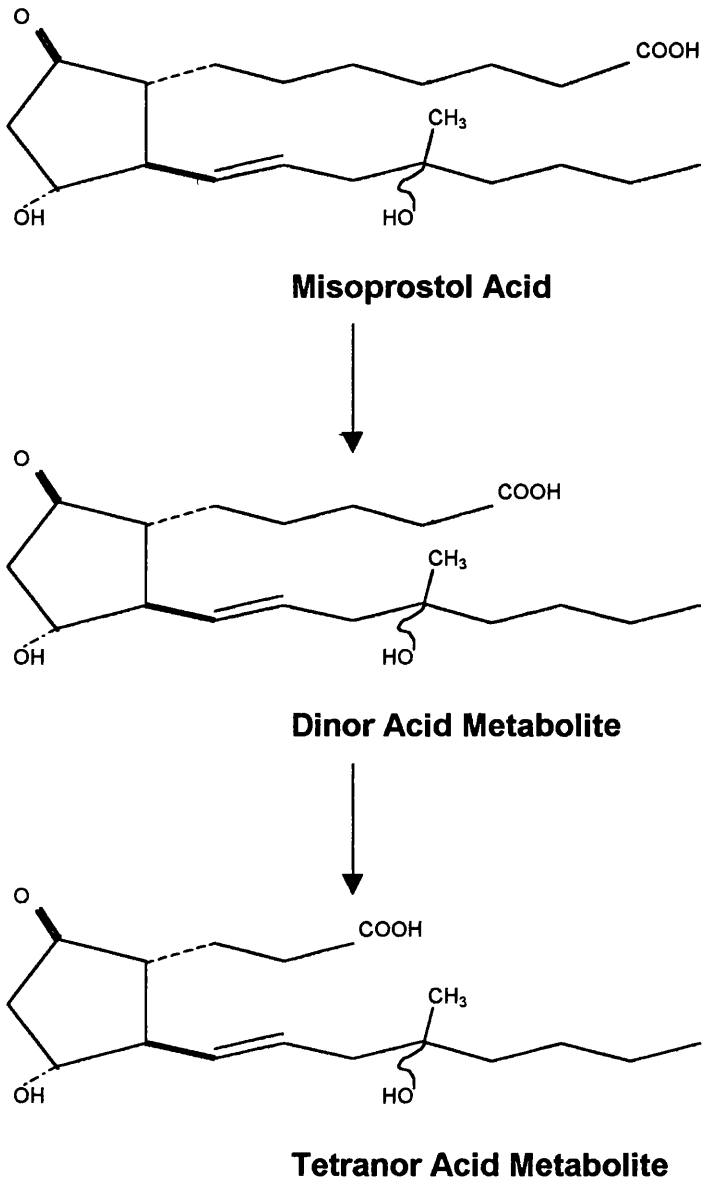


Figure 1.8. The biologically active misoprostol acid metabolite, and the inactive dinor and tetranor acid metabolites



Chapter 2

Postpartum uterine contractility in response to different doses of oral misoprostol.

Background

At this stage, it was important to understand the physiological response of the uterus in the puerperal state to orally administered misoprostol, and the nature of the uterine response to different doses of the drug. It was essential to confirm that misoprostol exerts a uterotonic action in the third stage of labour, to find out the interval to onset of action, and to interpret dose-response interactions. A physiological study was conducted aiming to investigate the effect of various dosages of oral misoprostol on uterine contractility in the immediate postpartum period, intrauterine pressure being used as a measure of uterine contractility.

Interest in intra-uterine pressure (IUP) began in the 1930's and 1940's as a means of investigating primary dysmenorrhea, which was thought to occur as a result of abnormal uterine activity (Moir, 1936; Woodbury *et al.*, 1947). Williams and Stallworthy (1952) were the first to develop the fluid-filled intrauterine pressure catheter (FFIUPC) which could be passed transcervically into the uterus, thereby making the measurement of intrauterine pressure practical in routine clinical practice. Knoke *et al.* (1976) reported the first systematic assessment of the accuracy of IUP measurement by concurrently recording it using three different FFIUPC's passed simultaneously into the same uterus, on nine women in labour. Although there were some variations in the measured pressure between the three catheters, the total uterine activity measured over a period of several hours was comparable.

Akerlund *et al.* (1978) advocated the superiority of the micro-transducer catheter over the fluid-filled open-ended catheters. They compared a micro-transducer catheter with the conventional fluid-filled open-end catheter to investigate

myometrial activity in the non-pregnant human uterus, both in vivo and in vitro. Both catheters gave identical intrauterine pressure recordings, but the micro-transducer catheter had additional advantages of being easily introduced through the cervix, not getting obstructed, and providing a much higher frequency response.

The Sonicaid (Gaeltec) catheter was investigated by Steer *et al.* (1978) who demonstrated its accuracy in measurement of IUP. They compared measurements obtained by the Sonicaid catheter with those obtained using an FFIUPC connected to an external transducer, on a series of four cases. The average mean discrepancy in measured IUP was 6.8 mm.Hg (Range of 5 to 7.4 mm.Hg), and the average percentage discrepancy was 13.6 (Range of 8.8% to 18%, 95% CI -26% to +34%). Random variations of up to 10% in measured IUP were reported to occur as a result of physiological variables. Since then, IUP has been used as a measure of uterine contractility in various studies; either using a micro-balloon (Bygdeman *et al.*, 1979), an open-end fluid-filled catheter, or the highly sensitive micro-transducer catheter (Akerlund *et al.*, 1978; Ulmsten & Andersson, 1979). Catheter-tip pressure transducers have been repeatedly used to measure IUP in various obstetric circumstances, such as in the assessment of the progress of induction or augmentation of labour (Arulkumaran, 1994; Haththotuwa & Arulkumaran, 1996), and has been accepted as a reliable and accurate means of providing information on intrauterine activity.

Chua *et al.* (1992) investigated the accuracy of IUP measurement in labour by using two catheter-tip pressure transducers (Sonicaid-Gaeltec). Twenty women were randomly allocated to two groups; in the first group, the two catheters were tied together with sterile catgut so that the tips of the two catheters remained

adjacent at all times, and probably located within the same amniotic fluid compartment in the uterus. In the second group the two catheters were introduced in different directions, such that each catheter tip was in a different amniotic fluid compartment. Although differences of up to 4.0 - 5.3 kpa (30 - 40 mm.Hg) occurred between some contractions, the mean difference in active contraction pressure between the two catheters was very small (0.52 - 0.53 kpa; 3.9 - 4.0 mm.Hg) and was not clinically significant. In spite of variations in the pressures of individual contractions when assessed by each catheter in the same uterus, cumulative active pressure was similar wherever the catheter tip was located, and there was little systematic difference in the overall active pressure measured by the two catheters. Steer (1993) confirmed that active pressure values for individual contractions, when measured simultaneously by two or more intra-uterine catheters, may vary by up to 50%, but this variation was not systematic, and cumulative measures were almost similar varying by less than 5%.

Although measurement of IUP has a limited place in routine use during labour, it has an established place as an experimental tool in physiological studies. The uterine response to different drugs has been repeatedly investigated, whether in-vitro on uterine muscle strips (Anderson *et al.* 1975), or in-vivo in non-pregnant conditions, during labour (Petrie *et al.* 1976), or in animal studies (Johnson *et al.* 1975).

Intrauterine pressure measurements have also been used to investigate the effect of breast feeding on uterine contractility, and in investigating the efficacy and stability of different uterotonic preparations. There are two main approaches to assess uterine contractility in the third stage of labour and the immediate postpartum period; the first method involves measurement of changes in placental

venous pressure, which is an indirect and cumbersome method, with difficult reproducibility, the second method involves measurement of IUP by an intrauterine pressure catheter.

Irons *et al.* (1994) used changes in placental venous pressure to assess uterine contractility in response to nipple stimulation, as a physiological means of management of the third stage of labour. Placental venous pressure was monitored by a pressure recorder calibrated to mm.Hg and connected to an external transducer. Uterine activity was therefore measured by using the placenta as an in-situ hydrostatic bag, and was reflected by the rise in placental venous pressure. When compared with routine syntometrine injection, 15 min. of nipple stimulation within a few seconds of delivery induced a higher rise in placental venous pressure (103 mm.Hg compared to 70.8 mm.Hg, p-value = 0.04).

A similar study investigating the influence of breast feeding and nipple stimulation on uterine contractility in the third stage of labour was conducted by Chua *et al.* (1994). No prophylactic oxytocic was given for third stage management, and a transducer-tipped catheter was inserted into the uterus immediately after delivery of the placenta. Uterine activity was measured for a control period of thirty minutes, after which the baby was put to the breast (n = 5), or the mother stimulated her nipple manually (n = 6) for a further 30 minutes. This was followed by an additional 30-min. post-stimulation observation period. Uterine activity during the stimulation period was then compared with the pre-stimulation and post-stimulation periods. An increase in uterine contractility of 17 to 730% was found during breast feeding or nipple stimulation. The highest increase in uterine contractility occurred in women who breast-fed compared to

women in the nipple-stimulation group; the median percentage increase amounting to 93% and 66% respectively.

Uterine contractility has also been used to investigate the efficacy and stability of different uterotonic preparations. Chua *et al.* (1993) investigated the clinical efficacy of Methergine (methylergometrine) and Syntocinon stored at high temperatures on postpartum uterine contractility. The drugs were evaluated after being stored at three different temperatures; 32°, 37°, and 42°C over a period of one year. The effect of each drug on uterine activity was tested after being stored for 3, 6, 9, and 12 months. Postpartum uterine activity was measured using a transducer-tipped catheter, and was monitored for a control period of 30 min. immediately after delivery of the placenta, followed by another 30 min. following drug administration. The increase in uterine activity was found to be highest among women receiving oxytocics stored at the recommended storage temperature.

Intrauterine pressure changes seem to correlate to blood loss in the third stage of labour. Chua *et al.* (1996) investigated IUP changes in the third stage of labour to correlate uterine activity with the amount of postpartum blood loss. IUP was measured using a calibrated Gaeltec catheter-tipped pressure transducer inserted into the cervix within 5 min. of delivery of the placenta, among 27 women over two hours. The third stage of labour was actively managed with oxytocics and controlled cord traction in 17 women, and physiologically in the rest. Blood loss over the same time period was collected on absorbent paper then quantitatively measured in the laboratory by calorimetric determination of haemoglobin content. Although no clinical correlation was found, it appeared that, as total uterine activity decreased, total blood loss increased.

In a more recent study, Chua *et al.* (1998) confirmed the reliability of the Gaeltec intrauterine catheter-tip transducers in measuring uterine activity in the third stage of labour, in spite of minor variations in individual active pressure recordings. Using the same methodology as their previous study (1992), 20 women were randomly allocated into two groups of ten. In the first group, the tips of two catheters were tied together with sterile catgut to keep their tips adjacent at all times, then were inserted transcervically into the uterine cavity after delivery of the placenta. In the second group the two catheters were independently inserted into the same uterine cavity; the first catheter was pushed into the uterus until it was felt to impinge on the fundus, while the second was slightly withdrawn away from the tip of the first catheter. Individual active pressure readings from the separate transducers were comparable, whether the catheters were tied up or were separate. Cumulative active pressure was very similar when assessed by each catheter in the same uterus.

Intrauterine pressure changes in response to misoprostol have been scarcely assessed in the literature. Uterine contractility after misoprostol administration was first reported among abortion patients. Norman *et al.* (1991) reported that oral misoprostol increased uterine activity in early pregnancy irrespective of the dosage used. They investigated uterine contractility in early pregnancy induction of abortion (under 56 days amenorrhoea) using misoprostol alone, then after pre-treatment with mifepristone. IUP was measured by means of a flexible transducer-tipped (Gaeltec) catheter, passed transcervically, and monitored for 30 min. before administration of oral misoprostol, and for the next three hours. In the first part of the study, the effect of 3 different doses of misoprostol alone was investigated; 200 μgm (n = 3), 400 μgm (n = 6), and 600 μgm (n = 3). All doses produced a significant increase in IUP, but regular uterine activity failed to

develop. The highest increase in IUP occurred with the 600 μgm dosage, but was not statistically significant. Another group of patients (n = 21) were pre-treated with 200 mg of mifepristone 48 hours before misoprostol administration. Baseline IUP readings were obtained over 30 min., after which a single oral misoprostol dose was administered; 200 μgm (n = 4), 400 μgm (n = 10), 600 μgm (n = 7). IUP was then monitored for a further three hours or until abortion occurred. A significant increase in total uterine activity occurred after misoprostol administration, which led to complete abortion in 18 of the 21 women in this group. The increase in IUP was highest after 30 min. of drug administration, then decreased gradually. No significant differences in uterine activity among the three different misoprostol dosages were reported.

The effects of Misoprostol on uterine contractility have also been studied at term before induction of labour. Neto *et al.* (1988) investigated uterine activity patterns after administration of 200 and 400 μgm of misoprostol orally, and 200 μgm vaginally in women with intrauterine fetal death at term. The onset of uterine activity in response to misoprostol was reported to vary between 10 to 120 min. of drug administration.

It was decided to investigate the effect of oral misoprostol on the uterus in the immediate postpartum period. In this study uterine activity is employed as an indirect guide to the uterine response to misoprostol, as a measure of its potential efficacy in the management of the third stage of labour. The aim of this study was to assess the effect of different doses of oral misoprostol on postpartum uterine contractility, the onset and duration of action of each dosage and its associated side effects, following normal vaginal delivery and after delivery of the placenta,

on a group of women who had undergone physiological management of the third stage of labour.

Patients and Methods

This was an observational study on 26 women with a single, normal, term pregnancy. They had normal vaginal deliveries, and no antenatal or intrapartum complications, after spontaneous labours not requiring induction or augmentation with oxytocin or prostaglandins. The third stage was managed physiologically, no uterine massage was performed, and no oxytocics were used. Informed consent was obtained in the first stage of labour. Women in the study were assigned into five treatment groups, each group receiving oral misoprostol in doses of 800, 600, 500, 400, or 200 μgm. The 800 μgm dosage was chosen to begin with because of its known clinical applications. The 200 μgm dosage was tested to see whether a clinical effect might be obtained at such a low dose. Any woman thought to have excessive blood loss was excluded from the study. Other exclusion criteria included multiple pregnancy, history of PPH in a previous pregnancy, or antepartum haemorrhage in the current pregnancy. This study was conducted at The National University Hospital, Singapore, because of their long track record of research using IUPC's, in collaboration with the department of Obstetrics and Gynaecology, UCH Medical School, UCL.

Measurement of Uterine Activity

Intrauterine pressure was measured using a calibrated transducer-tipped catheter (Gaeltec Ltd., Dunvegan, Scotland), which was introduced into the uterus within five minutes of delivery of the placenta. The catheter was calibrated according to

the instructions in the supplier's handbook (Oxford Medical, London, UK). It was then inserted transcervically into the uterine cavity, until its tip was felt to impinge on the uterine fundus, after which the catheter was connected to a Sonicaid Meridian fetal monitor (Sonicaid Ltd., Oxford Medical instruments, Chichester, U.K.) to record uterine activity profiles.

A control prestimulation recording of 30 minutes was made to obtain the baseline uterine activity for each woman. Following that, the designated dosage of Misoprostol was orally administered, and uterine activity was monitored for a further 90 minutes.

The amplitudes of contractions above 100 mm.Hg are not recorded by the monitor on the double-channel recording paper, but are digitally displayed. Therefore, the peak active pressure (in mm.Hg) shown for each contraction was manually recorded on the double-channel paper throughout the two-hour observation period. Uterine activity in each 10 minute period was manually calculated as cumulative active pressure in mm.Hg. The amplitude of uterine activity (average active pressure) every 30 seconds was calculated by subtracting the average basal tone from the peak pressure. After that, the active pressures were added up to obtain uterine activity in 10-minute intervals (Figure 2.1).

Earlier equipment used to have a built-in uterine activity module which used the information obtained from the IUP catheter to electronically compute uterine activity every 15 minutes. This value was both displayed in a window on the module and printed in figures on the double-channel recording paper against a vertical scale from 0 to 2500 k.pas/15 min. (Arulkumaran, 1994). Currently used equipment, however, lack this facility. The amplitudes of contractions above 100

mm.Hg are not marked on the double-channel recording paper and, therefore, have to be manually recorded. Cumulative active pressure is also manually calculated. However, a shorter 10-minute interval was chosen as a cut-point for active pressure calculation for early detection of spontaneous reductions in uterine activity.

To determine the effect of each dosage, mean uterine activity in the 90-minute period after administration of the designated dosage was compared with mean uterine activity during the 30 minutes pre-stimulation period prior to drug administration, each woman acting as her own control. The percentage change in uterine activity was thus calculated. The speed of onset of action of the designated dosage was measured from the time of administration of the drug to commencement of a recorded increase in the amplitude of uterine activity. The duration of action of the medication was defined as the period of time the mean uterine activity remained above the individual woman's baseline uterine activity. These definitions are in line with previous publications in this field.

Each patient's temperature, pulse, and blood pressure were obtained prior to drug administration, and at 30 minute intervals after that. Any side effects experienced by the patient following drug administration during the observation period were documented. Patients were continuously accompanied by an attendant throughout the observation period. The onset and duration of action of each tested dosage, in addition to all symptoms experienced by the patients, were meticulously recorded.

Statistical methods

Statistical analysis was performed using SPSS for windows (version 6.1, SPSS, Chicago, Illinois, USA). Continuous variables that are normally distributed are presented as means and standard deviations (SD), those that are not normally distributed are presented as medians and interquartile ranges (IQR). Uterine activity among the total study population was first calculated as means and standard deviations, then a paired sample t-test was performed to compare the mean increase in total uterine contractility before and after drug administration for the total population irrespective of the dosage used. Mean uterine contractility during the first 30 min. after misoprostol administration was compared among the five doses by analysis of covariance, using mean uterine contractility before drug administration as the baseline co-variate. The five treatment groups were then compared by linear contrast testing to investigate the effect of increasing dosage on uterine contractility, i.e. if there is a linear increase in contractility as a function of the increase in misoprostol dosage. Continuous variables that are not normally distributed and represent related data (eg. Temperature changes after misoprostol administration) were compared using the Wilcoxon signed rank test.

Results

The study population consisted of a total of 26 women who received different dosages of oral misoprostol. They were unequally distributed into five groups; 800 μgm (n = 8), 600 μgm (n = 5), 500 μgm (n = 4), 400 μgm (n = 4), and 200 μgm (n = 5). Maternal age of the total study population ranged from 20 to 36 years (mean = 27.55, SD = 4.8; median = 27.5, IQR = 23.8 – 31.3).

Uterine activity:

Table 2.1 demonstrates the effect of orally administered misoprostol on postpartum uterine contractility, and its onset and duration of action among the total study population. Misoprostol showed a fast onset (mean = 8.2 min., SD = 3.9; Median = 7.0 min., IQR = 4.7 – 10.8), and a prolonged duration of action (mean = 63 min., SD = 10.4; Median = 65.0 min., IQR = 57.5 – 75.0). Paired sample t-test showed a highly significant difference in mean contractility between the prestimulation phase and that following administration of the drug (p-value < 0.001). Irrespective of the dosage used, the mean difference between prestimulation contractility and that of the first 30 min. after drug administration for all groups combined is 246 (95% CI of 152-340), and was statistically significant (p-value < 0.001).

Table 2.2. demonstrates mean uterine contractility of the five dosage groups in the prestimulation (control) phase, and that in response to misoprostol during the first 30 min. following administration. All misoprostol dosages induced a change in uterine contractility compared to the control prestimulation phase. The observed values of the changes in uterine activity in each treatment group are plotted in Figure 2.2. The first 30 min. of drug administration showed the highest increase in uterine contractility, after which it was seen to fall in the subsequent one hour observation period. The largest increase in uterine activity was achieved with an oral dose of 600 μgm (382 mm.Hg), followed by the 500 μgm dosage (261 mm.Hg), then the 800 μgm dosage (237 mm.Hg). No statistically significant difference was found in mean uterine contractility following misoprostol administration among the five dosages (Analysis of covariance f-test = 1.98, p-value = 0.14).

Table 2.3 demonstrates the onset and duration of action of each misoprostol dosage. The fastest onset and longest duration of action of oral misoprostol was achieved with the 800 μgm dosage (5.5 min., IQR of 4.1 to 7.5, and 75 min., IQR of 66 to 84, respectively). The 400 μgm dosage appeared to have the slowest onset and shortest duration of action (12.6 min., IQR of 6.3 to 16.1, and 45 min., IQR of 40 to 65, respectively).

Figure 2.2. demonstrates average IUP changes before and after administration of each misoprostol dosage. Assessment of the effect of increasing misoprostol dosage on uterine contractility was carried out by testing for a linear increase in mean contractility during the 30 min. following drug administration as a function of the increase in dosage, which was found not to be statistically significant (f-test = 2.85, p-value = 0.11). When logarithmic transformation of the data was performed, analysis of co-variance also revealed no statistically significant differences in the ratios of mean increase in uterine activity (all p-values > 0.05) following all the doses of oral misoprostol. The uterotonic effect of misoprostol was therefore not dose related.

Figures 2.3, 2.4, and 2.5 show the outputs from the sonicaid monitor demonstrating IUP recordings before and after administration of 800, 200, and 500 μgm of oral misoprostol respectively.

Side Effects:

Any side effects occurring to women in the study were documented throughout the two-hour observation period. Side effects of each administered dosage are shown in Table 2.4. The most common side effect was shivering, which occurred

in 12 women (48%). It started between 12 to 88 min. after oral misoprostol administration, and lasted between 12 to 55 min. Shivering occurred in 20% of women receiving the 200 μgm dosage, in 50% of women receiving 500 μgm, 80% of women receiving 600 μgm, and 62.5% of women receiving the 800 μgm dosage. No shivering was seen among women in the 400 μgm group. The difference in the incidence of shivering between the dosages studied was statistically significant (p-value < 0.05).

The second most common side effect was pyrexia, which was defined as a rise in body temperature of 37.5°C or over, and occurred in 9 women (36.0%) (Table 2.5). All doses combined revealed a highly significant rise in temperature following drug administration (p-value < 0.001). The rise in temperature varied between 37.5°C to 39.4°C (median 38.7°C), occurring in 80% of women receiving the 600 μgm dosage, followed by 50% of those receiving 500 μgm, and 25% of those receiving 400 μgm. The difference in the incidence of pyrexia (> 37.5°C) between the studied dosages was statistically significant (p-value < 0.001). Other than the 800 μgm dosage group, it appeared that the rise in temperature may be dose related. Most of the women were not aware of the rise in temperature, which was noted to occur following the shivering.

However, one woman who received an 800 μgm dosage of oral misoprostol experienced shivering for about an hour, followed by severe hyperthermia and required vigorous treatment. She started to shiver thirteen minutes after receiving the tablets for about an hour, which was followed by a rise in temperature (rectal temperature of 41.9°C). Cooling was started by splashing ice water on the patient, then evaporating it with fans. Following that, ice packs were applied and the patient was covered by water-soaked sheets. Intravenous fluids (Normal Saline

0.9%) and Hartman's solution were started, and 100% oxygen was administered by mask. The patient was catheterised to monitor her renal output and to watch for myoglobinuria. Despite these measures, the patient's core temperature remained above 40°C. A nasogastric tube was then inserted, and ice saline lavage was started. After 30 minutes of lavage, the core temperature was brought down to 38.9°C and the lavage was stopped. However, cold sponging was continued until the patient's core temperature fell to 38°C, forty-five minutes later. Renal output after catheterisation was only 20 mL despite receiving 2.5 L of IV fluids, so the patient was given an IV bolus of 20 mg of furosemide, after which the urinary output increased and remained above 60 mL an hour, and the urine remained clear. The patient's rectal temperature returned to 37.3°C three hours and forty minutes after starting the hyperthermia treatment (Chong *et al.*, 1997).

Other minor side effects included uterine pain, which occurred in two women (7.7%); one in the 200 μgm and one in the 600 μgm dosage groups, in addition to nausea (12.5%) and dizziness (12.5%), both of which were reported with the 800 μgm dosage (Table 2.4).

Discussion and Conclusion

This study was conducted to investigate the effect of orally administered misoprostol on uterine activity in the immediate postpartum period, and to determine the optimum oral dose of misoprostol in terms of uterotonic effect and safety. Oral misoprostol was associated with a significant rise in uterine contractility in the postpartum period regardless of the dosage used. It has a very fast onset (7.2 min., IQR of 4.7 to 10.8) and a prolonged duration of action (65

min., IQR of 57.5 to 75.0), which is of special clinical relevance in the third stage of labour.

Catheter-tip pressure transducers have been used to measure intrauterine activity in the third stage of labour reliably and safely in various studies (Chua *et al.*, 1993, 1994; Forman *et al.*, 1982 a, b; Ingemarsson, 1989). In this study, participating women were used as their own controls to provide their own baseline uterine activity level before administering the designated oral misoprostol dosage. The change in uterine activity after drug administration should therefore be an accurate measure of the uterotonic effect of each dose. However, it was fundamental to account for biological variations in uterine activity by establishing each individual's baseline uterine activity before administering the drug, which explains the reason for administration much later than in usual circumstances.

In our small study population, there was a highly significant increase in uterine contractility after oral misoprostol administration (p-value < 0.001). All the dosages tested were associated with an increase in uterine contractility compared to the prestimulation phase, and doses as small as 200 μgm of orally administered misoprostol were shown to have a uterotonic effect. Although Norman *et al.* (1991) also failed to demonstrate a dose-dependent effect to misoprostol in abortion patients, it has been clinically proven that different doses of misoprostol lead to different clinical outcomes, e.g. in induction of labour, abortion, or miscarriage, which highlights the limitations of this technique.

On the whole, side effects observed with oral misoprostol were mild. The two most prominent side effects were shivering (48%) and pyrexia (36%). There was

a significant rise in temperature following drug administration among the total study population (p-value < 0.001). This remained significantly high (p-value < 0.001) even after exclusion of the one case who developed severe hyperthermia after receiving an 800 μgm dosage from data analysis.

None of the other commonly reported side effects of prostaglandins such as nausea, vomiting, or diarrhoea were experienced by any of the patients. Few women complained of uterine pain, which might have been due to the gradual nature of the increase in uterine contractility associated with prostaglandin E_1 administration (Crowshaw, 1983). Apart from shivering and pyrexia, there were no statistically significant differences in the incidence of side effects between the different dosages.

Although the 400 μgm dosage appeared to be associated with the least change in uterine contractility and the lowest incidence of side effects, and the 800 μgm dosage appeared to have the lowest incidence of pyrexia (12.5%), these findings may not necessarily represent the true situation due to our small sample size. The 800 μgm dosage group contained the one case who developed severe hyperthermia, but was excluded from data analysis. The small number of patients in each dosage group, therefore, prevents the drawing of strong conclusions.

The 600 μgm dosage induced the highest change in contractility, but was associated with a high incidence of shivering and pyrexia. The 500 μgm dosage was associated with strong uterine contractility and moderate incidence of side effects.

In spite of our small sample size, this study revealed that oral misoprostol leads to an increase in postpartum uterine contractility irrespective of the dosage used, shivering and pyrexia being the most common side effects. However, the explanation to why some women shivered and some did not, remains unknown. It could be that the occurrence of shivering may be an idiosyncratic reaction in some patients after receiving misoprostol, and may not even be dose-related.

Pyrexia, on the other hand, is a well recognised centrally mediated side effect of prostaglandins (Milton & Wendlandt, 1971; Veale & Cooper, 1975; Jain & Mishell, 1994; Haberal *et al.*, 1996; Creinin *et al.*, 1997 a, b; Srisomboon *et al.*, 1997 a). However, hyperpyrexia or hyperthermia (defined as a rise in body temperature to 41.1°C and above, with accompanying central nervous system signs) may lead to grave, life-threatening consequences. In hyperpyrexia cases, severe muscle contraction results in rhabdomyolysis (muscle destruction) with an accompanying increase in serum myoglobin and myoglobinuria. Furthermore, as a result of destruction of red blood cells and intravascular haemolysis, haemoglobin is released into the blood stream. Circulating free haemoglobin and myoglobin in the plasma is commonly complicated by acute renal failure. Hyperpyrexia will ultimately lead to shock, cerebral damage and death (Samiy *et al.*, 1987). The issue of pyrexia and shivering, and their association with oral misoprostol administration in the third stage of labour will be discussed in a later chapter in this thesis.

The definite uterotonic effect oral misoprostol demonstrates on the postpartum uterus supports the idea that it may be used to enhance contractility of the uterus for active management of the third stage of labour and prevention of PPH.

Table 2.1. Effect of orally administered misoprostol on uterine contractility (all doses combined)

Effect of oral misoprostol	Mean (SD)	Median (IQR)
Uterine contractility[1]		
Prestimulation phase	553 (220)	528 (396-651)
Contractility in first 30 min.[2]	797 (210)	819 (687-941)
Contractility in 2nd 30 min.	684 (237)	640 (557-858)
Contractility in 3rd 30 min.	486 (169)	488 (372-624)
Onset of action (min.)	8.2 (3.9)	7.2 (4.7-10.8)
Duration of action (min.)	63 (10.4)	65 (57.5-75.0)

1. P-value < 0.001
2. Mean difference in contractility between the first 30 minutes and the prestimulation contractility for all groups combined is 246 (95% CI of 152-340), which was statistically significantly (p-value < 0.001).

Table 2.2. Effect of different dosages of oral misoprostol on uterine contractility before and after administration (values are mean (SD) or mean [SE])

Dose	n	Pre-stimulation contractility	Contractility during the first 30 min. after misoprostol administration	Difference* [SE]	Change in uterine activity in first 30 min.	p-value
200	5	575 (115)	803 (179)	228 [112]	1.40	0.11
400	4	449 (133)	554 (239)	104 [63]	1.23	0.20
500	4	509 (218)	770 (228)	261 [153]	1.51	0.19
600	5	539 (349)	921 (242)	382 [135]	1.70	0.04*
800	8	620 (233)	850 (106)	230 [69]	1.39	0.01*

* No significant difference was found between the 5 doses (p-value = 0.14)

Table 2.3. Onset and duration of action of different dosages of orally administered misoprostol

Misoprostol Dosage	n	Onset of action	Duration of action
		Median (IQR)	Median (IQR)
200 ugm	5	8.8 (8.6-10.8)	60 (37.5-70)
400 ugm	4	12.6 (6.3-16.1)	45 (40-65)
500 ugm	4	8.4 (4.6-15.7)	65 (60-85)
600 ugm	5	7.5 (6.0-10.2)	65 (55-75)
800 ugm	8	5.5 (4.1-7.5)	75 (66-84)

* Based on the time it took for uterine activity to return to pre-drug levels.

Table 2.4. Side effects of different dosages of orally administered misoprostol

Side effect	200 ug No. %	400 ug No. %	500 ug No. %	600 ug No. %	800 ug No. %	Total No. %
Shivering*	1 (20.0)	0	2 (50.0)	4 (80.0)	5 (62.5)	12 (48.0)
Temp>37.5°C**	1 (20.0)	1 (25.0)	2 (50.0)	4 (80.0)	1 (12.5)	9 (36.0)
Uterine pain	1 (20.0)	0	0	1 (20.0)	0	2 (7.7)
Nausea	0	0	0	0	1 (12.5)	1 (4.0)
Dizziness	0	0	0	0	1 (12.5)	1 (4.0)

* The difference in the incidence of shivering between the studied dosages was statistically significant, p-value < 0.05

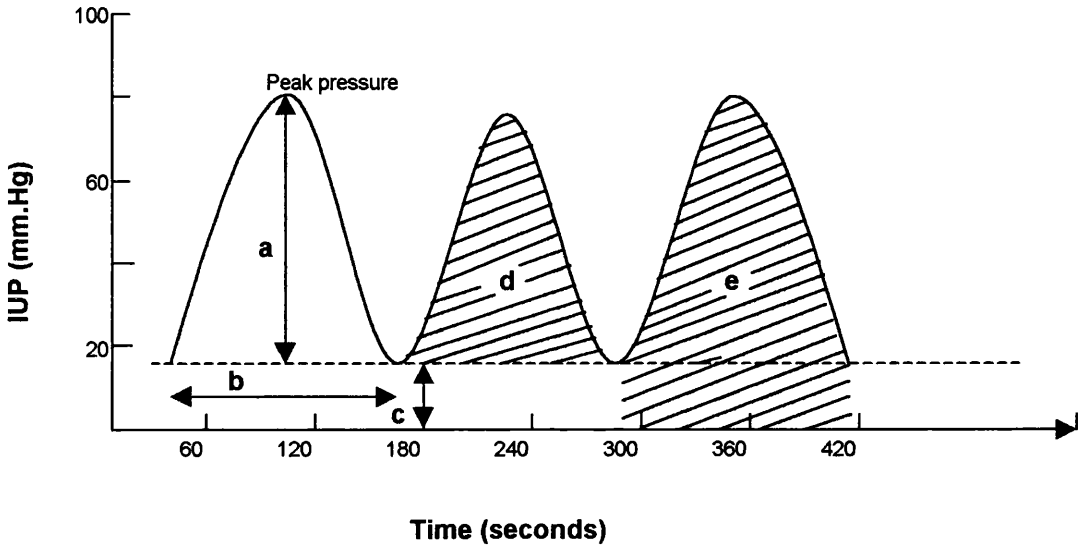
** The difference in the incidence of pyrexia (> 37.5°C) between the studied dosages was statistically significant, p-value < 0.001

Table 2.5. Rise in temperature associated with different dosages of orally administered misoprostol in the third stage of labour

Misoprostol Dosage	Temperature before administration[a]	Temperature after administration[b]	Difference	p-value
	Median (IQR)	Median (IQR)		
All groups*	37.2 (36.8-37.4)	37.5 (37.0-38.4)	0.3	< 0.001
200 μgm	37.0 (36.8-37.4)	37.1 (37.0-37.4)	0.1	0.72
400 μgm	37.2 (36.1-37.8)	37.5 (36.5-38.3)	0.3	0.11
500 μgm	37.3 (37.0-37.7)	37.8 (37.1-38.2)	0.5	0.06
600 μgm	37.3 (37.3-37.4)	38.9 (38.4-39.1)	1.6	0.07
800 μgm*	36.6 (36.5-36.9)	37.0 (36.8-37.2)	0.4	0.18

a Temperature measured after delivery prior to drug administration.
b Temperature measured 2 hours after delivery.
* Hyperpyrexia case excluded from analysis.
** The difference in the incidence of pyrexia (> 37.5°C) between the studied dosages was statistically significant, p-value < 0.001

Figure 2.1. Method of calculating uterine activity



a: active pressure or amplitude

b: duration of contraction

c: basal tone

d: active contraction area

e: total contraction area

* The amplitude of uterine activity (active pressure) every 30 seconds was calculated by subtracting the average basal tone from the peak pressure. After that, the active pressures were added up to obtain uterine activity in 10-minute intervals.

Figure 2.2. Average uterine pressure before and after administration of each misoprostol dosage

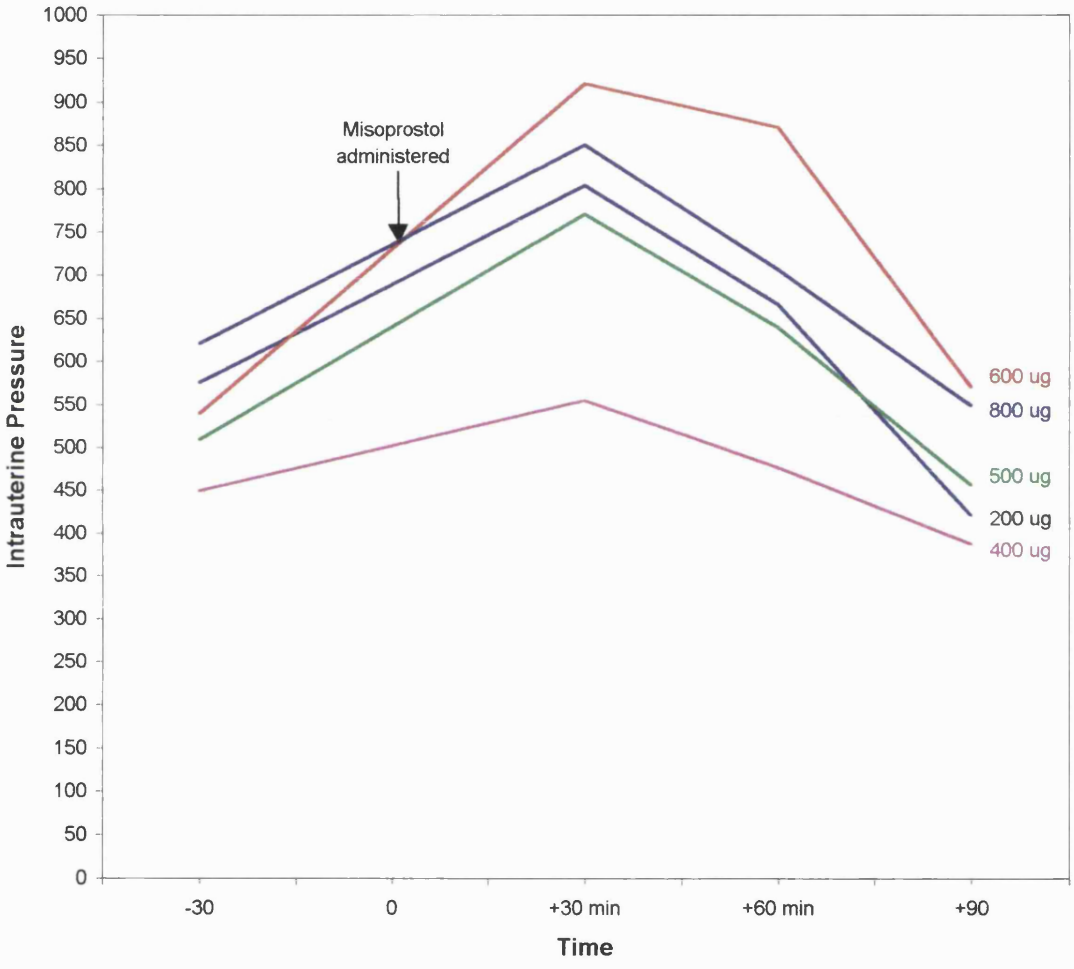


Figure 2.3. Output from the sonicaid monitor demonstrating IUP recording before and after administration of 800 μgm of oral misoprostol

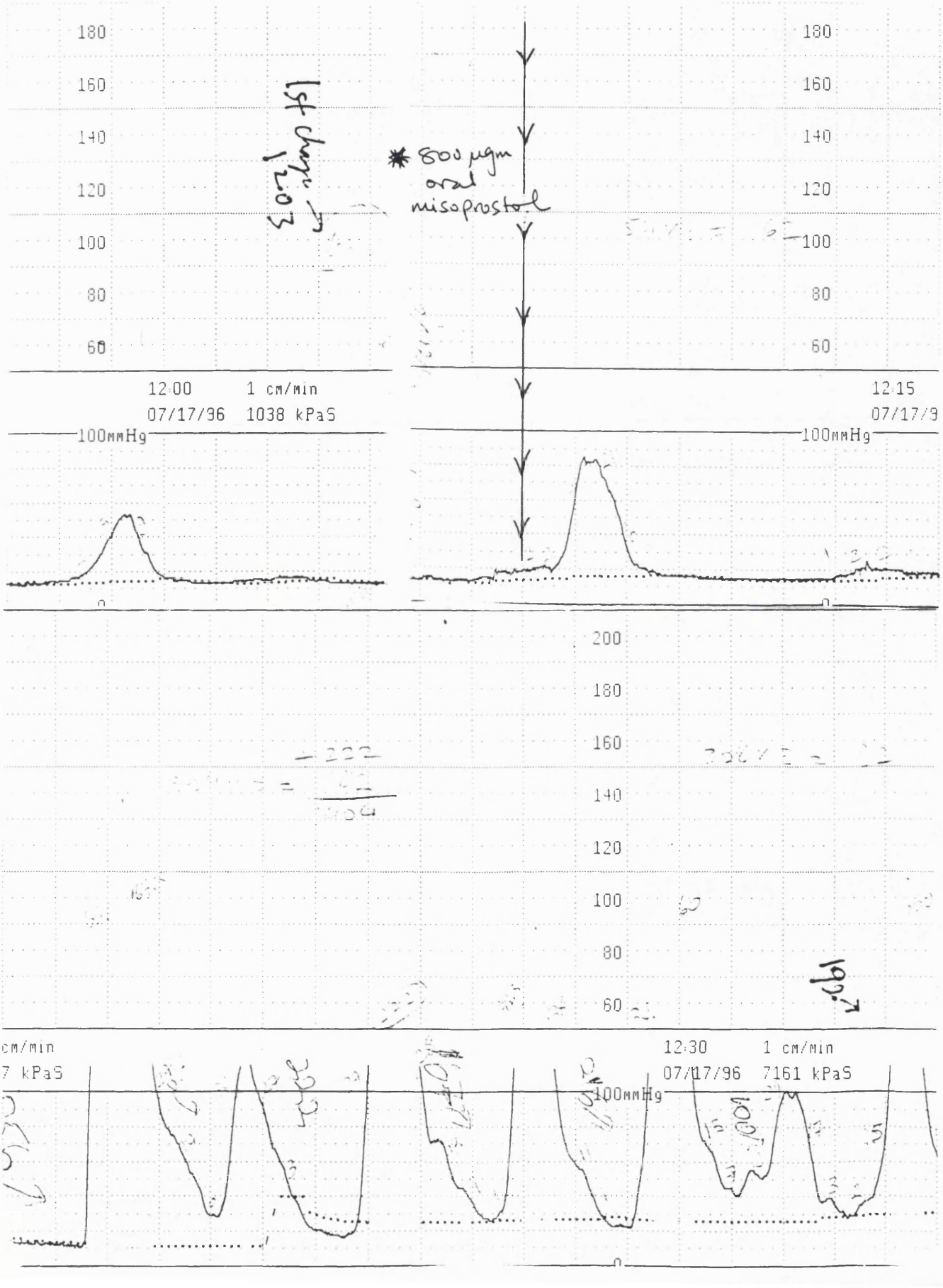


Figure 2.4. Output from the sonicaid monitor demonstrating IUP recording before and after administration of 200 μgm of oral misoprostol

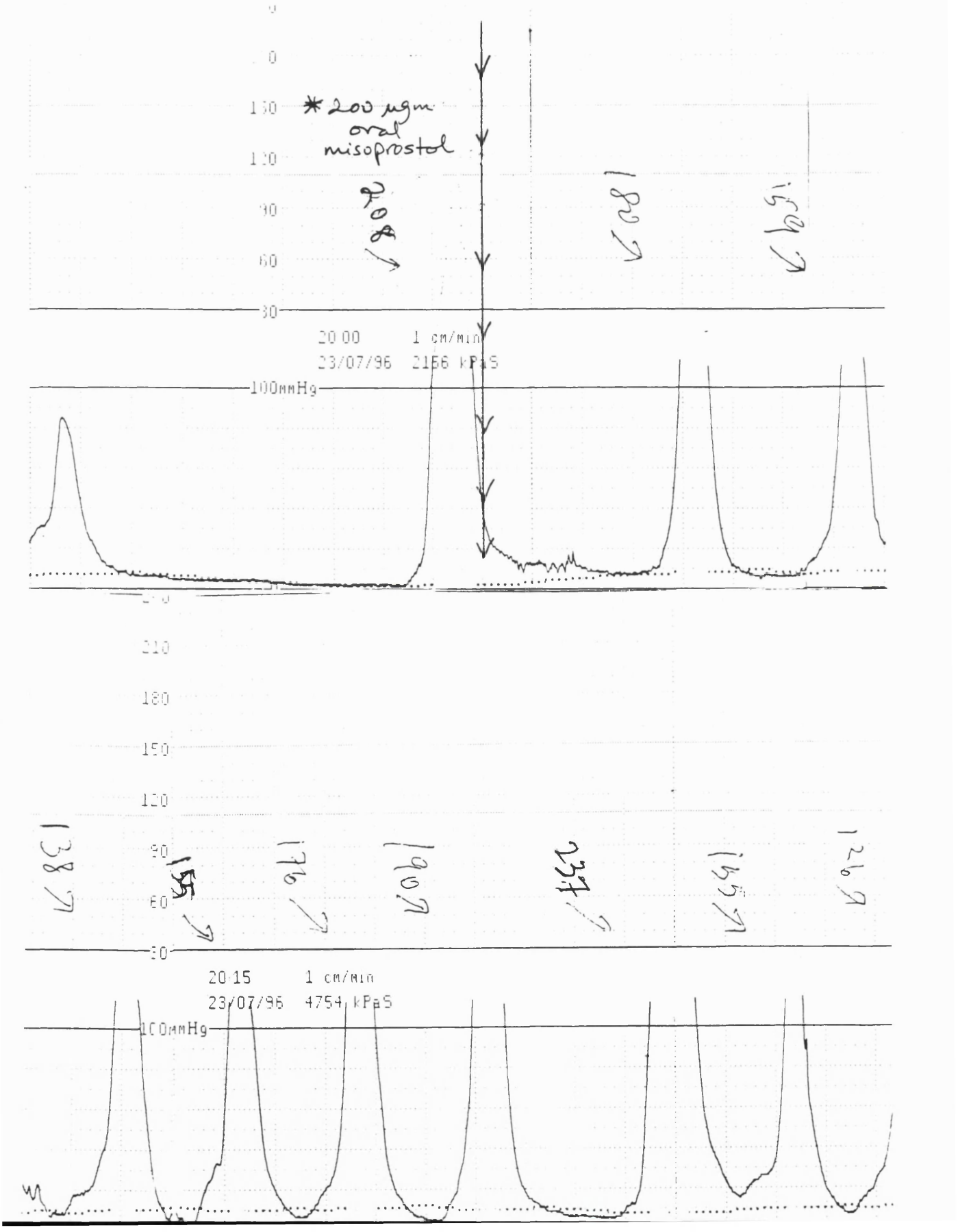
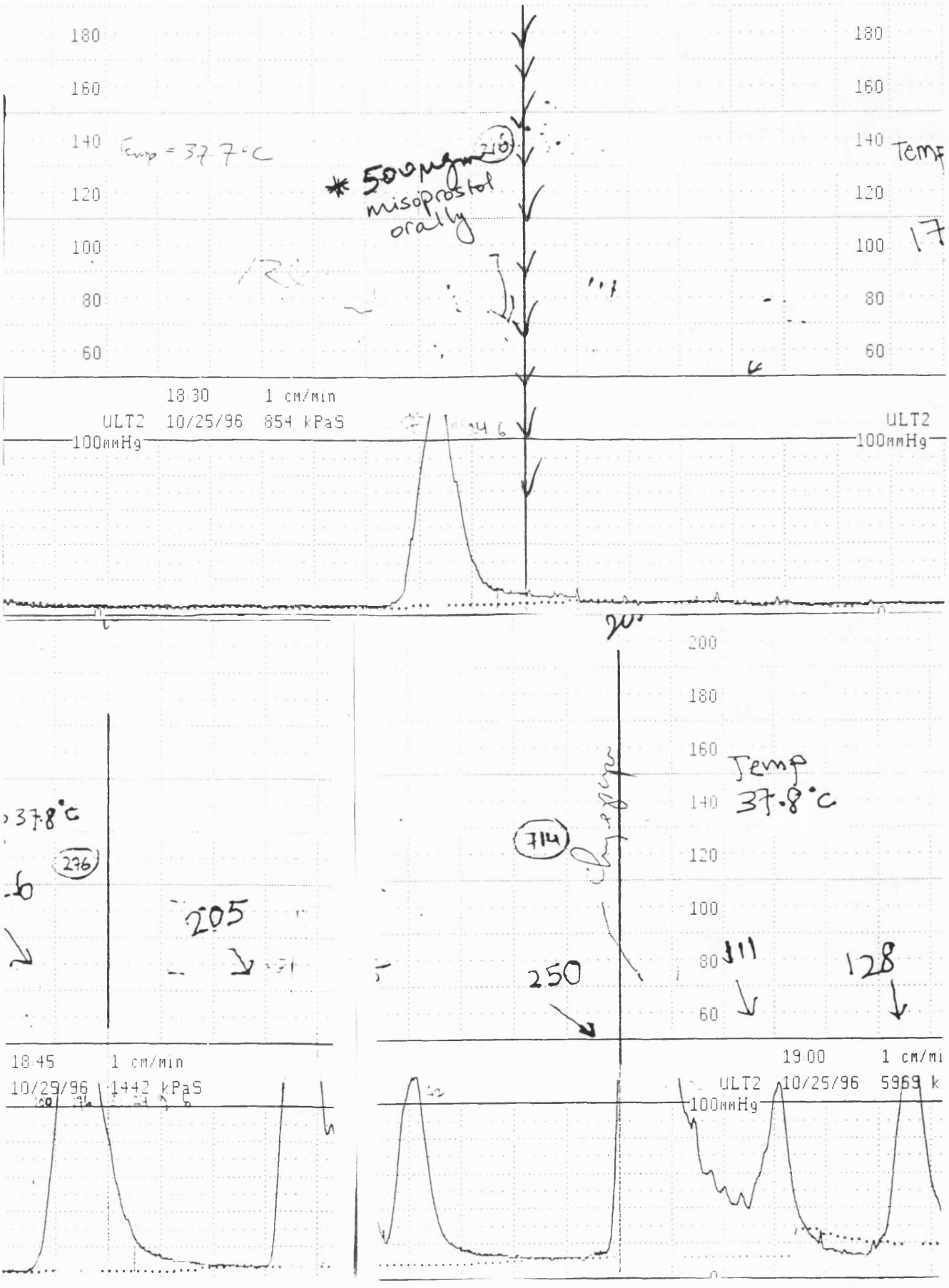


Figure 2.5. Output from the sonicaid monitor demonstrating IUP recording before and after administration of 500 μgm of oral misoprostol



Chapter 3

Clinical studies identifying the efficacy and side effects of different dosages of oral misoprostol in the third stage of labour.

Background

There has never been any attempt at using prostaglandins orally for prophylactic management of the third stage of labour. Scientific dogma indicated that oral absorption of any medication would be too slow to act quickly enough for prevention of PPH. The only attempt examining the oral approach for prophylactic management of the third stage of labour was that by De-Groot *et al.* (1996), investigating the use of oral methylergometrine, which was not found to be an appropriate alternative to parenteral oxytocics. It was associated with unpredictable pharmacokinetic and dynamic properties, and demonstrated no clinical effect in reducing postpartum blood loss.

The concept of using misoprostol as a prophylactic agent for management of the third stage of labour arose from its confirmed uterotonic properties and their application in various obstetric circumstances. The physiological intrauterine pressure study confirmed that oral misoprostol has a powerful uterotonic effect when used in the postpartum period. To ascertain whether misoprostol would be successful as a prophylactic oxytocic agent in the third stage of labour, a randomised controlled clinical trial would have to be conducted to determine its efficacy in comparison with other oxytocics proved to be effective in this field.

Doubts about the efficacy of oral misoprostol, however, led us to approach this work carefully. With an ethical viewpoint, preliminary observational studies had first to be conducted to investigate the efficacy of different misoprostol dosages. The appropriate effective dosage, associated with the least side effects, that could safely and ethically be used in a randomised trial had to be determined. This was implemented by means of two consecutive observational pilot studies.

The choice of misoprostol dose to be used in the pilot study was a central issue, since the appropriate dosage required to achieve the desired clinical response with minimum side effects was uncertain. Successful choice of an accurate dosage depends on a balance of three main factors; the clinical indication, efficacy to achieve the desired outcome, and minimisation of side effects. The issue of choice of dosage of misoprostol for a specific clinical indication has been a problem that is clearly highlighted by different studies in the literature. When used in the treatment of gastroduodenal ulcers, a dosage of 1200 μgm of oral misoprostol, administered in divided doses over 24 hours, was found to be safe, well tolerated, and associated with minimal side effects (Herting & Nissen, 1986; Collins 1990). However, when used in the third trimester of pregnancy, a relatively small dose of 50 μgm of misoprostol administered vaginally could successfully induce labour in 79% of cases (Marguilies *et al.*, 1992). First trimester abortion studies indicate that sole administration of misoprostol dosages up to 800 μgm without mifepristone leads to partial or complete abortion in only 11% of cases, (Rabe *et al.*, 1987), and when used after pre-treatment with mifepristone, the success rate rises to over 90% (Aubeny & Baulieu, 1991). Aubeny and Baulieu (1991) demonstrated that a single oral dose of 400 μgm of misoprostol, administered following pre-treatment with 600 mg of mifepristone, followed 3 hours later by an additional 200 μgm, achieved successful abortion in 97.6% of women between 42 and 49 days of amenorrhea, but expulsion of the products of conception within 4 hours occurred in only 69% of cases. In second trimester abortion, oral misoprostol doses of up to 800 μgm have been reported to achieve a 30% success rate, and doses up to 1200 μgm achieve a 77% successful abortion rate, following pre-treatment with 600 mg of mifepristone (El-Refaey *et al.*, 1993).

The safety of single doses of 200 μgm of misoprostol and total daily doses of 800 μgm has been established in previous studies. At first, lower doses of 200 and 400 μgm were used for fear of side effects, after which an 800 μgm dosage was used in later studies.

In a study investigating the use of misoprostol in second trimester abortion (El-Refaey *et al.*, 1995 a), an 800 μgm dosage was administered vaginally, followed by subsequent 400 μgm oral doses at three hourly intervals, up to a maximum of four doses, achieved a 95% successful abortion rate. Nulliparous women were found to require a higher dosage than multiparous women; 2000 μgm (1200 - 2400 μgm) compared to 1200 μgm (800 - 1600 μgm) respectively. Reported side effects were mainly gastrointestinal. Nausea occurred in 50% of patients, 40% had vomiting, 15% required antiemetic therapy, 20% reported having mild diarrhoea, and 45% developed pyrexia. Side effects were reported to occur more frequently among nulliparous women as a result of the higher dosage they received.

El-Refaey and Templeton (1994 b) demonstrated the efficacy of 800 μgm of oral misoprostol whether administered as a single dose or divided into smaller dosages in early abortion. In a randomised study, an 800 μgm dosage of oral misoprostol was administered to 150 women undergoing early abortion (56 days gestation or less), after pre-treatment with mifepristone. Women first received 200 mg of mifepristone, followed 36 to 48 hours later with either a single oral dose of 800 μgm of misoprostol or two sequential doses of 400 μgm administered two hours apart. The overall success rate was 93.3% (95% CI of 89.3 to 97.3). The higher single dose achieved a 95% success rate, compared to 92% with the sequential regimen, but the difference was not statistically significant (p-value = 0.52).

Gastrointestinal side effects occurred more frequently among patients receiving the single oral dosage; vomiting in 40%, nausea in 68%, and abdominal pain in 36% of patients, compared to 31%, 59% and 39% respectively among those receiving the sequential regimen, but the differences were not statistically significant. Diarrhoea occurred in 33% of women receiving the single higher dose, compared to 21% in the second group, and was significantly higher both in incidence (p-value = 0.049) and severity (p-value = 0.034). The larger dosage of misoprostol was associated with a small but significant fall in blood pressure within four hours of drug administration (p-value = 0.025). Although it appeared that administration of the drug in a sequential manner may decrease the frequency of side effects, but it was noted that, other than diarrhoea, the frequency of side effects did not differ significantly between the two studied groups.

In another study, El-Refaey and Templeton (1995 b) compared a 600 μgm dosage of misoprostol administered orally and vaginally, and demonstrated its efficacy in achieving second trimester pregnancy termination. In a randomised study of 70 women undergoing mid-trimester abortion, 600 μgm of misoprostol was administered 36 to 48 hours after pre-treatment with 600 mg of oral mifepristone. In the first group, women received all the doses vaginally; the initial 600 μgm dosage, followed by 400 μgm doses every three hours. In the second group, women received the first dose of 600 μgm vaginally, followed by the 400 μgm in oral doses administered every three hours. Dosages of up to 2200 μgm were used over a 12-hour interval and were well tolerated. The median dosage used for the first group was 1000 μgm, and that for the second group was 1400 μgm. The overall success rate of the two groups was similar; 97% (CI of 90 to 100%). Side effects reported were vomiting (57% versus 61%) and diarrhoea (29% versus 35%), which were not significantly different between the two studied groups.

In miscarriage, the combination of mifepristone and 600 μgm of oral misoprostol has been shown to have a success rate of 93%. El-Refaey *et al.* (1992) demonstrated the efficacy of this dosage in the management of missed abortion and anembrionic pregnancy. Women first received a single oral dose of 600 mg of mifepristone, followed 36 to 48 hours later by 600 μgm of misoprostol, administered orally in a divided dose of 400 μgm, followed two hours later by a further 200 μgm. Successful abortion was achieved in 84.3% (43/51) of patients after receiving that dosage. A dosage lower than 600 μgm, however, might not have been sufficient to achieve the desired outcome, while a higher dose might have been associated with unacceptable side effects.

The disparity in the response of the uterus to misoprostol may be explained by variations in uterine responsiveness to prostaglandins at different gestations, in addition to the route of administration of the drug, which is an important consideration. It also appears that the incidence of gastrointestinal side effects increases the higher the dosage administered. The incidence of vomiting, for example, is 10% with an oral misoprostol dose of 400 μgm (Aubeny & Baulieu, 1991), which increases to 40% with an 800 μgm dosage (El-Refaey & Templeton, 1994 b).

A major problem that faced us with these studies was in accurate determination of the most important outcome variable; postpartum blood loss. Accurate assessment of blood loss in the third stage of labour was a very important factor in predicting the success of these studies. As discussed in the Introduction (chapter 1), discrepancies among reports of PPH rates occur as a result of the different methods used for blood loss measurement, whether quantitatively or visually (Newton *et al.* 1961; Brant, 1967; Razvi *et al.*, 1996). However, subjective

estimation of blood loss in parturient women is still the most common method applied in the UK. Major studies in the literature investigating management of the third stage of labour have used subjective assessment of blood loss to report rates of PPH. In line with other landmark papers (Nieminen & Jarvinen, 1963; Dumoulin, 1981; Prendiville *et al.*, 1988; Begley, 1990; McDonald *et al.*, 1993; Mitchell & Elbourne, 1993; Khan *et al.*, 1995; Yuen *et al.*, 1995), we have also employed clinical assessment of postpartum blood loss in our studies.

The first pilot study was a prospective observational study investigating the efficacy of 600 μgm of orally administered misoprostol for management of the third stage of labour and prevention of PPH. This particular dosage was chosen to begin with, on the basis of previous abortion studies using misoprostol orally. The main objective of this study was to investigate the rate of PPH in a group of women receiving 600 μgm of oral misoprostol at the end of the second stage of labour, and to assess the associated clinical effects of its use for management of the third stage of labour. Two hundred and thirty seven (237) consecutive women were recruited for this study.

Results of the first pilot study revealed a high incidence of shivering, which was the main side effect. This incited us to investigate whether the incidence of shivering was dose related. It was therefore decided to follow the first pilot study up with a second study in which smaller misoprostol dosages were used.

The second pilot study was also an observational study that examined the rate of PPH and perceived incidence of side effects in two further groups of women receiving two lower doses of oral misoprostol; 400 and 500 μgm. A further two hundred and eight (208) women were recruited for this study (103 received 400

μgm, and 105 received 500 μgm doses). These two groups were then compared with the first group who had received the 600 μgm dosage, in terms of PPH rate, events in the third stage of labour, and side effects associated with each dosage.

Patients and methods

The study protocols were reviewed and approved by the local Ethics Committee. Information sheets (Appendix A) explaining the aims of the studies were distributed to potential participants in antenatal classes, antenatal clinics, and the Day Assessment Area. On admission to the labour ward women were reminded of the study, and written Informed Consent was obtained if they still wished to participate (Appendix A).

The main objective of the first pilot study was to estimate the incidence of primary PPH among women receiving 600 μgm of oral misoprostol (3 tablets of 200 μgm each). Blood loss during delivery and prior to leaving the labour ward was estimated clinically by the attendant midwife or obstetrician, immediately after delivery of the baby and clamping and dividing the cord. PPH was defined as an estimated blood loss (EBL) of 500 mL or more during the first 24 hours after delivery. Any delayed haemorrhage within the first 24 hours was also documented.

Since clinical assessment of blood loss was subjective, other objective indices of blood loss were also recorded, such as the need for blood transfusion, change in haemoglobin concentration and haematocrit, need for therapeutic oxytocics, length of the third stage, and need for manual removal of the placenta. Other

secondary outcomes investigated included the incidence of severe PPH (≥ 1000 mL) or secondary PPH (after 24 hours), and the need for subsequent evacuation of retained products of conception. The change in haemoglobin concentration and packed cell volume was calculated, especially among women who had an instrumental delivery and/or estimated blood loss of 500 mL or more (compared to values obtained in labour or from a late pregnancy blood test, if done within two weeks of delivery). At first, we aimed to obtain a blood sample in labour and two days postpartum from all women recruited to the study for comparison purposes. However, since this is not the usual practice at our hospital, many women declined these tests (see discussion). Otherwise, it is routine practice at our hospital to obtain a blood sample in labour for women about to undergo an instrumental delivery, and again two days postpartum for both women who had an instrumental delivery, and those who had a PPH.

Potential adverse effects including the incidence of hypertension (defined as diastolic blood pressure > 100 mm.Hg or systolic blood pressure > 150 mm.Hg) were documented on a specially designed form, which also included demographic data and information related to the type and circumstances of delivery (Appendix A). The last measured blood pressure and temperature before birth, and one hour after delivery were also documented on the data collection form, which was completed by the midwife attending each woman.

In the second pilot study two further doses of misoprostol were investigated; 400 and 500 μgm. Both doses were compared to the 600 μgm dosage in terms of PPH rates, third stage variables, and associated side effects. The primary aim of the second pilot study, in addition to finding out the rate of PPH associated with the 400 and 500 μgm doses, and the secondary outcomes investigated in the first pilot

study, was to investigate and compare the incidence and potential side effects of the three misoprostol dosages.

Side effects investigated in both pilot studies were nausea, headache, hot flushes, dizziness, vomiting, tiredness, diarrhoea, abdominal pain, and shivering. To elicit self perception of the incidence and severity of side effects, a questionnaire with points rating of each symptom, ranging from 0 (none) to 4 (very severe) was completed by self-assessment one hour after delivery before leaving the labour ward (Appendix B).

The principle criteria for exclusion from both pilot studies were: placenta praevia, multiple pregnancy, intrauterine fetal death, gestational age less than 32 weeks, previous history of PPH, and women in their sixth or more pregnancy. In both pilot studies, women with hypertension, pre-eclampsia, or pregnancy induced hypertension, in addition to those whose haemoglobin in pregnancy was less than 10 were all excluded.

In both pilot studies, the misoprostol tablets were orally administered, immediately after delivery of the baby and clamping of the cord, and before delivery of the placenta. In the first pilot study women were asked to swallow 600 μgm of misoprostol (three tablets). In the second pilot study women received either 400 μgm (two tablets) or 500 μgm (two and a half tablets). Syntometrine was not given but midwives were instructed to do so if they felt that there was a clinical indication. Otherwise, the delivery of the placenta was managed actively, according to hospital policy. Two days after delivery, a sample of venous blood for haemoglobin and haematocrit assessment was obtained from women,

specifically those who had had an instrumental delivery, or postpartum blood loss of 500 mL or more.

Statistical methods

Statistical analysis was performed using SPSS for windows (version 6.1, SPSS, Chicago, Illinois, USA). Categorical variables are summarised as numbers and percentages, whereas continuous variables that are normally distributed are presented as means and standard deviations (SD). Continuous variables that are not normally distributed are presented as medians and interquartile ranges (IQR) or geometric means and 95% reference range (95% RR). The paired *t*-test was used to compare values of systolic and diastolic blood pressure, haemoglobin, haematocrit, and temperature before and after delivery. The association between two categorical variables was assessed using Chi-square testing. The significance level was set at 5%. Comparisons of means and percentages among the three dose groups were conducted using the F-test, and the chi-square test respectively. Due to the rarity of the side effect as reported by the patients, the rating from moderate to severe (levels 2, 3 & 4) were combined. Adjusted analysis was done by logistic regression to control for baseline demographic and labour variables that might have differed in the population of each group prior to drug administration.

3.1. Pilot study 1: Use of 600 μgm of oral Misoprostol for routine management of the third stage of labour

Results

Two hundred and thirty seven women (237) were consecutively recruited to receive 600 μgm of oral misoprostol. The demographic characteristics and labour variables of these patients are summarised in Table 3.1.1 and Table 3.1.2 respectively. Recruited women had a mean age (SD) of 29.1 (5.8) years, 113 patients (48%) were primigravidae, 47 (20%) patients underwent induction of labour, 112 women (47%) used epidural anaesthesia, and 72 (30%) required syntocinon augmentation. Episiotomy was performed for 52 patients (22%), and 106 (45%) had first or second-degree tears.

The median length of the third stage of labour was 5 minutes (IQR of 4 to 7). Thirteen patients (6%) had an estimated blood loss (EBL) equal to or above 500 mL. Only 6 (3%) of these had an EBL above 500 mL, and none had an EBL of 1000 mL or more. Secondary PPH did not occur in any case. The median EBL for all the study population was 200 mL (IQR of 150 to 300 mL). Four women (2%) required a manual removal of the placenta (MROP), and four (of 175 or 2%) had a postnatal haemoglobin concentration ≤ 9 g/dL. Two women required a blood transfusion; one had a broad ligament haematoma, which was conservatively managed, and the other received the transfusion during MROP. The effects of 600 μgm of oral misoprostol on the third stage of labour and its associated side effects are summarised in Table 3.1.3.

Gastrointestinal side effects were infrequent. Forty women (17%) complained of nausea, vomiting occurred in 19 women (8%) during the first hour after delivery, and seven women (3%) reported loose stool during the first 24 hours after delivery. These symptoms were mild and did not require any treatment. Shivering was the most prominent side effect, having been reported by 148 women (62%). This was self limiting, starting approximately twenty minutes after swallowing the tablets and lasted for 10 to 25 minutes. There were no cases of infection and no patient required surgical evacuation of the uterus.

Comparison of the last measured systolic and diastolic blood pressure before delivery with that measured one hour after delivery revealed a mean reduction of 1.0 (SE = 0.9) and 0.8 (0.6) mm.Hg respectively, but neither were statistically significant. Similarly haemoglobin, haematocrit and temperature were compared before and after delivery, all are summarised in Table 3.1.4. A reduction of 0.3 (0.15) g/dL in haemoglobin concentration and of 0.01 (0.005) in haematocrit were marginally significant (p-value = 0.06 and p-value = 0.047, respectively). Temperature significantly increased by 0.5 (0.05)°C (SE 0.05, p-value < 0.001).

3.2. Pilot study 2: Comparison of the efficacy of three misoprostol dosages; 400, 500, and 600 μgm, for management of the third stage of labour, and examining the perceived incidence of side effects of each dosage

The main side effect associated with the 600 μgm dosage of oral misoprostol in the first pilot study was shivering. It was therefore decided to follow the first pilot study with a second pilot study in which smaller misoprostol dosages; 400 and 500 μgm, were used, to investigate whether the incidence of shivering was dose dependant, and to identify the efficacy of smaller doses of oral misoprostol in the prevention of PPH.

Results

One hundred and three (103) and one hundred and five (105) women received the 400 and 500 μgm doses of oral misoprostol respectively. The demographic characteristics of women in both groups, in addition to those of women who received the 600 μgm dosage are summarised in table 3.2.1. No significant difference was found among the three groups in any of these characteristics.

Table 3.2.2 demonstrates a summary of labour variables among the three groups, no difference was found among the studied groups in labour variables. However, among women receiving the 400 μgm dosage, there was a higher percentage of epidural analgesia in labour (57%), and first and second-degree tears (59%). On the other hand, the 600 μgm dose group showed a higher percentage of patients

with instrumental vaginal deliveries (28%), although this was not statistically significant (chi-square = 5.02, p-value = 0.08).

Unadjusted comparison of outcomes of the three doses:

The effect of misoprostol on the management of the third stage of labour by each dose administered is summarised in table 3.2.3. Although the percentage of patients with an EBL ≥ 500 mL was lowest among women in the 600 μgm group (6%), compared to 8% in those receiving 500 μgm, and 12% in the 400 μgm group, no statistical significance was reached (chi-square = 3.80, p-value = 0.15). The 600 μgm group showed a significantly lower mean estimated blood loss (Geometric mean = 202 mL, 95% RR of 62 to 656), lower mean time length of the third stage of labour (5.0 min, 95% RR of 2 to 13), and a lower percentage of women requiring further syntometrine administration than the other two arms (5%, compared to 16% in the 400 μgm group, and 14% in the 500 μgm group). The ratio of the geometric mean estimated blood loss, geometric mean time length of the third stage of labour, and the ratio of the percentage of patients requiring further syntometrine administration for the 600 μgm group to the other two groups were 0.81, 0.87, and 0.36 respectively (95% CI of (0.73 to 0.90), (0.78 to 0.97), and (0.19 to 0.71)).

The last measured systolic and diastolic blood pressure before delivery was compared with that measured one hour after delivery. Temperature was similarly compared before and after delivery. All are summarised in Tables 3.1.4, 3.2.4 and 3.2.5. Among women receiving the 400 μgm dosage, there was a mean reduction of 2.0 (SE = 1.2) mm.Hg in systolic BP, and 0.7 (1.1) mm.Hg in diastolic BP, but neither were statistically significant. Temperature significantly increased by 0.6

(0.08)°C (p-value < 0.001). Women receiving the 500 μgm dosage also had a mean reduction in systolic BP of 1.3 (SE = 1.3) mm.Hg, and in diastolic BP of 0.9 (1.1) mm.Hg, but neither were statistically significant. A significant increase in temperature by 0.7 (0.09)°C (p-value < 0.001) was also seen in this group.

b. Unadjusted comparisons of side-effects of the three doses:

Patients' perception of the side effects of oral misoprostol by treatment group is summarised in table 3.2.6. On the whole, the group receiving the 400 μgm dosage showed a smaller percentage of patients with a mild to severe side effect. In this group only 9% of patients had mild to severe nausea. This was against 22% and 17% in the 500 and 600 μgm groups respectively (chi-square = 6.01, p-value = 0.05). A clear difference was found among the three groups in their perception of shivering, being reported by 41% of patients receiving the 400 μgm dosage, against 62% among those receiving 500 μgm, and 62% among those receiving the 600 μgm dosage (chi-square = 21.7, p-value < 0.001).

c. Adjusted comparisons of outcomes and side-effects:

The adjusted comparisons of the outcomes of management of the third stage of labour among the three dosage groups, and the adjusted comparisons of the perceived side effects are summarised in table 3.2.7. The adjusted results mainly agree with the crude ones demonstrated in tables 3.2.3 and 3.2.4. However, since women in the 600 μgm group had a higher percentage of instrumental vaginal deliveries, adjusting for this factor as well as all other demographic and labour variables in relation to blood loss showed a clear significant difference between the 600 μgm group and the other two groups. For example, the adjusted ratio of

the rate of patients with EBL of 500 mL and above in the 400 μgm group is 2.67 that of the 500 μgm group (95 CI of 1.1 to 6.46). The adjusted result in relation to the side effects was very similar to the crude one, mainly showing lower side effects between the 400 μgm group and the 600 μgm groups.

Discussion

These two pilot studies are the first to describe the use of oral misoprostol in the management of the third stage of labour and prevention of PPH. Oral misoprostol has been shown to be effective in lowering the rate of PPH when used in the third stage of labour. On the whole, the rates of PPH, need for further therapeutic oxytocics, and the length of the third stage of labour were lower than those reported with physiological management, and are comparable to results obtained with syntometrine (Keirse *et al.*, Cochrane database of systematic reviews, 1995). Although both pilot studies were observational and not a randomised trial, their results suggest that misoprostol may be an effective oral prophylactic oxytocic drug, that could be used in the third stage of labour and prevention of PPH.

The estimated PPH rate was lowest among women receiving the 600 μgm dosage of oral misoprostol (6%), compared to 8% in those receiving the 500 μgm dosage. The highest PPH rate (12%) occurred among women receiving the 400 μgm dosage. The need for further therapeutic oxytocics and the length of the third stage of labour was lowest with the 600 μgm oral misoprostol dosage. Although it appears that the 12% PPH rate obtained with the 400 μgm oral misoprostol dosage is comparable to PPH rates associated with the use of saline or placebo in some third stage studies (Poeschmann *et al.*, 1991; De Groot, 1996), it is lower than that reported with physiological management in the Bristol third stage trial (Prendiville *et al.*, 1988).

In the first pilot study using the 600 μgm oral misoprostol dosage, 2% of women had a postnatal haemoglobin concentration ≤ 9 g/dL, and there was a reduction of 0.3 (SE of 0.15) g/dL in haemoglobin (Hb) concentration (p-value = 0.06), when

compared to pre-delivery values. These values are lower than that reported with syntometrine, syntocinon, PG 15-methyl $F_{2\alpha}$ (Carboprost), and physiological management (Thilaganathan *et al.*, 1993; Yuen *et al.*, 1995; Chua *et al.*, 1995). Thilaganathan *et al.* (1993) compared active management of the third stage of labour, using syntometrine and controlled cord traction, with physiological management among low risk women. Active management was associated with a fall in Hb of 0.5 g/dL (IQR of -0.1 to 1.2), compared to 0.7 g/dL (IQR of -0.3 to 1.4) with physiological management, and only 1 woman (of 103 or 1%) had a postpartum Hb under 9 g/dL compared to 5 (of 90 or 6%) in the physiological management group. Chua *et al.*, (1995) compared the use of 0.5 mg of syntometrine with 125 μgm of PG 15-methyl $F_{2\alpha}$ (Carboprost) in the third stage of labour, and reported similar changes in Hb levels after drug administration in the two groups. Mean maternal Hb fell from 12.3 g/dL (range of 9.8 to 14.5) to 11.4 g/dL (range of 8.1 to 13.2) after delivery with PG 15-methyl $F_{2\alpha}$, and from 12.3 g/dL (range of 8.3 to 14.7) to 11.4 g/dL (range of 8.6 to 14.3) with syntometrine. Yuen *et al.* (1995) compared the use of IM syntometrine with syntocinon for the management of the third stage of labour, and reported a fall in Hb of 1.2 g/dL (IQR of 0.3 - 2.3) with syntometrine and 1.5 g/dL (IQR of 0.6 - 2.4) with syntocinon, from pre-delivery values.

The efficacy of oral misoprostol in lowering postpartum blood loss may well be dose-dependant. The group receiving the 600 μgm dosage of oral misoprostol showed a significantly lower mean estimated blood loss, lower mean length of the third stage of labour, and less patients required additional therapeutic oxytocics than the other two groups, but was associated with a higher incidence of side effects. This agrees with results of the intrauterine pressure study (chapter 2)

where the higher dosages induced a greater change in uterine contractility, but were associated with a higher frequency of side effects.

The use of prophylactic syntometrine in the third stage of labour is associated with its known hypertensive effect. Due to the pilot nature of both observational studies, patients with high blood pressure were excluded. Nevertheless, no hypertensive effects were identified with any of the three oral misoprostol dosages among women who were normotensive before labour. The frequency of vomiting, the most distressing symptom women experience with syntometrine, reported among the three dosages remained almost half that reported when syntometrine is used (McDonald *et al.*, 1993; Prendiville *et al.*, 1988).

In general, patients' perception of misoprostol at this early stage of development was positive but needed to be assessed more thoroughly. Gastrointestinal side effects were infrequent, mild and did not require any treatment. Furthermore, a side effect of misoprostol that has not been previously described in the literature was identified. Shivering was seen to occur in 62% of patients receiving the 600 and 500 μgm dosages, and in 41% of patients receiving the 400 μgm dose. However, although it was annoying to some, it was not regarded as serious morbidity. Another side effect was a rise in temperature, which was seen with all three studied dosages. Temperature significantly increased by 0.5°C, 0.6°C, and 0.7°C among women receiving the 600, 400, and 500 μgm dosages, respectively.

The incidence of shivering as a side effect of oral misoprostol was recognised in the course of both observational studies and during the physiological intrauterine pressure study. In the field of abortion, the use of larger misoprostol dosages was not associated with this side effect (El-Refaey & Templeton, 1994 a, b; 1995 b).

Shivering is a recognised symptom that is known to occur during or immediately after normal delivery. In older textbooks, shivering was thought to occur in response to passage of amniotic fluid into the maternal circulation during labour (Bruniquel, 1963), however, many people did not accept this theory. Jaameri *et al.* (1966) reported a shivering rate of 22.7% among women with normal deliveries, and it was seen to occur in the immediate postpartum period. Shivering is known to increase in association with epidural anaesthesia, during which its incidence rises up to 33 to 60% of cases (Brownridge, 1986; Morgan *et al.*, 1984). In both observational studies there was no significant difference in the incidence of shivering between patients who had epidural anaesthesia and those who had not. The occurrence of shivering and rise in temperature in association with oral misoprostol will be discussed in a later chapter in this thesis.

An important source of bias for both pilot studies lies in the method of assessment of blood loss, as the midwives and clinicians did that subjectively by clinical evaluation. Clinical assessment of blood loss may be inaccurate but, on the other hand, quantitative laboratory assessment techniques for measurement of blood loss are cumbersome, and increase the cost and duration of clinical studies. In this study, highly experienced midwives and clinicians estimated blood loss. Nonetheless, possible inaccuracies might have been introduced as a result of blood being diluted by amniotic fluid or lost on swabs or drapes, or simple observer bias, which may have affected the results to a certain extent. However, these inaccuracies would probably have occurred in the same proportion among the three dosages investigated. Another source of bias lies in the fact that people assessing blood loss and collecting the data were not blind to the hypothesis under investigation, or to the dosage of misoprostol given.

Another point of weakness was in quantifying the fall in haemoglobin and haematocrit concentration after delivery. Ideally, the prenatal blood sample should have been obtained from all women during labour, for accurate comparison with the postnatal blood sample two days after delivery. At first, whilst evaluating the efficacy of the 600 μgm oral misoprostol dosage in the first pilot study, we aimed to obtain a blood sample in labour and two days postpartum from all recruited women. However, since this is not the usual practice at our hospital, many women declined these tests, especially during labour. When a blood sample in labour could not be obtained, we looked for values from late pregnancy blood tests (if done within two weeks of delivery) for comparison purposes. Otherwise, it is routine practice at our hospital to obtain a blood sample in labour for women about to undergo an instrumental delivery, and again two days postpartum for both women who had an instrumental delivery, and those who had a PPH. Therefore, we ended up with only 76 pairs of pre-and post-delivery blood samples for comparison; which represents only 32% of the total study population. Therefore, due to the difficulty in obtaining maternal blood samples, we discontinued evaluating the drop in haemoglobin and haematocrit with the 400 and 500 μgm oral misoprostol dosages in the second pilot study.

In spite of both pilot studies being observational, with relatively small numbers of patients, their results impart that misoprostol may be an effective agent for the prophylactic management of the third stage of labour and prevention of PPH, that is associated with few side effects. It was revealed, however, that further work is required to ascertain the efficacy of misoprostol by comparing it to other currently used oxytocics for prophylactic management of the third stage of labour, by means of a randomised controlled clinical trial.

Table 3.1.1. Demographic characteristics of women receiving 600 μgm of oral misoprostol for third stage management

Demographic variables	n = 237
Mean (SD) maternal age (years)	29.1 (5.8)
Mean (SD) Maternal weight (kg)	76.3 (11.5)
Mean (SD) Maternal height (cm)	163.2 (6.7)
Number (%) of primigravidae	113 (48)
Mean (SD) Gestational age at delivery (weeks)	39.7 (1.4)

Table 3.1.2. Labour variables of women receiving 600 μgm of oral misoprostol for third stage management (values are given as n (%) or mean (SD), as appropriate)

Labour variables	n = 237
Spontaneous onset of labour	190 (80)
Syntocinon augmentation	72 (30)
Epidural analgesia in 1st or 2nd stage	112 (47)
Narcotic analgesia in 1st or 2nd stage	90 (38)
Episiotomy	52 (22)
First and Second degree tears	106 (45)
Instrumental vaginal delivery	67 (28)
Length of 1st stage (hours)	6.7 (3.9)
Length of 2nd stage (mins.)	66 (60)
Birthweight (kg)	3.30 (0.5)

Table 3.1.3. Effect of 600 ugm of oral misoprostol on the third stage of labour

Third stage variables	n = 237
Number (%) with blood loss ≥ 500 mL	13 (6)
Number (%) with blood loss ≥ 1000 mL	0 (0)
Median (IQR) of blood loss (mL)	200 (150 - 300)
Number (%) with manual removal of placenta	4 (2)
Number (%) with repeat syntometrine injection	12 (5)
Number (%) with systolic BP ≥ 150 (mm.Hg)	2 (1)
Number (%) with diastolic BP ≥ 100 (mm.Hg)	0 (0)
Number (%) with postnatal haemoglobin < 9 (g/dL)	4 (2)
Median (IQR) third stage length (min.)	5 (4 - 7)
Number (%) with third stage length ≥ 30 min.	1 (0.5)
Number (%) who experienced nausea	40 (17)
Number (%) who vomited	19 (8)
Number (%) who had diarrhoea	7 (3.2)
Number (%) who shivered	148 (62)

Table 3.1.4: Blood pressure, haemoglobin and temperature measurements before and after delivery among women receiving 600 ugm of oral misoprostol for third stage management (values are means (SD))

	n	Before delivery	After delivery	Mean Difference [SE]	p-value
Systolic BP (mm.Hg)	184	119.3 (13)	118.4 (12)	-1.0 [0.9]	0.25
Diastolic BP (mm.Hg)	184	73.8 (8)	73.0 (8)	-0.8 [0.6]	0.20
Haemoglobin (g/dL)	76	11.3 (0.9)	11.0 (1.3)	-0.3 [0.15]	0.06
Haematocrit	73	0.34 (0.03)	0.33 (0.04)	-0.01 [0.005]	0.047
Temperature (°C)	182	36.6 (0.4)	37.1 (0.7)	0.5 [0.05]	<0.001

Table 3.2.1. Comparison of demographic characteristics of women receiving 400, 500, or 600 μgm of oral misoprostol for third stage management (values are means and (SD))

Demographic Characteristic	400 μgm n = 103	500 μgm n = 105	600 μgm n = 237	p-value
Age (years)	29.4 (6.0)	29.7 (5.8)	29.1 (5.8)	0.68
Weight (kg)	76.5 (13.7)	75.0 (9.8)	76.3 (11.5)	0.75
Height (cm)	163.7 (7.4)	162.0 (7.2)	163.2 (6.7)	0.29
Gestational age (wks)	39.6 (1.4)	39.5 (1.5)	39.7 (1.4)	0.47
Number (%) primigravidae	47 (52)	43 (49)	113 (48)	0.84

Table 3.2.2. Comparison of labour variables of women receiving 400, 500, or 600 μgm of oral misoprostol for third stage management

Labour variables	400 μgm n=103	500 μgm n=105	600 μgm n=237	p-value
Spontaneous onset of labour	76 (75%)	79 (76%)	190 (80%)	0.56
Syntocinon augmentation	31 (30%)	27 (28%)	72 (30%)	0.79
Epidural analgesia	59 (57%)	47 (45%)	112 (47%)	0.17
Narcotic analgesia	48 (46%)	42 (42%)	90 (38%)	0.63
Episiotomies	18 (18%)	25 (24%)	52 (22%)	0.48
1st or 2nd degree tears	59 (59.8%)	50 (45%)	106 (45%)	0.20
Instrumental deliveries	20 (19%)	19 (18%)	67 (28%)	0.08
Geometric mean (95%RR) of length of 1st stage (hour)	5.9 (1.8-19.4)	4.8 (1.1-21.7)	5.5 (1.5-21.0)	0.10
Geometric mean (95%RR) of length of 2nd stage (hour)	0.53 (0.05-6.1)	0.55 (0.06-7.5)	0.55 (0.05-6.8)	0.94
Mean (SD) birthweight (kg)	3.4 (0.5)	3.3 (0.5)	3.3 (0.5)	0.69

Table 3.2.3. Comparison of the effect of 400, 500, or 600 μgm of oral misoprostol on the third stage of labour

Third stage variables	400 μgm n = 103	500 μgm n = 105	600 μgm n = 237	p-value
EBL ≥ 500 mL.	12 (12%)	8 (8%)	13 (6%)	0.15
EBL ≥ 1000 mL.	1 (1%)	0	0	0.23*
Geometric mean (95% RR) of EBL (mL)	252 (79-801)	247 (91-672)	202 (62-656)	<0.001
Manual removal of placenta	0	2 (2%)	4 (2%)	0.56*
Repeat syntometrine injection	13 (16%)	10 (14%)	12 (5%)	0.008
Geometric mean (95% RR) of third stage in (min)	5.8 (2-18)	5.7 (2-18)	5.0 (2-13)	0.04
Systolic BP > 150 mm.Hg	0	0	2 (1.0%)	1.00
Diastolic BP > 100 mm.Hg	0	0	0	1.00

*Generalised fisher exact test

Table 3.2.4. Blood pressure and temperature measurements before and after delivery among women receiving 400 μgm of oral misoprostol for third stage management (values are means (SD))

	n	Before delivery	After delivery	Mean Difference [SE]	p-value
Systolic BP (mm.Hg)	82	118.2 (13)	116.2 (11)	-2.0 [1.2]	0.10
Diastolic BP (mm.Hg)	82	72.8 (8)	72.1 (8)	-0.7 [1.1]	0.54
Temperature (^{o}C)	71	36.7 (0.4)	37.4 (0.7)	0.6 [0.08]	<0.001

Table 3.2.5. Blood pressure and temperature measurements before and after delivery among women receiving 500 μgm of oral misoprostol for third stage management (values are means (SD))

	n	Before delivery	After delivery	Mean Difference [SE]	p-value
Systolic BP (mm.Hg)	82	115.8 (10)	114.5 (12)	-1.3 [1.3]	0.32
Diastolic BP (mm.Hg)	82	72.7 (8)	71.8 (9)	-0.9 [1.1]	0.41
Temperature (^{o}C)	71	36.5 (0.4)	37.2 (0.8)	0.7 [0.09]	<0.001

Table 3.2.6. Comparison of the side effects of the three misoprostol dosages

Side effects	400 µgm n=103	500 µgm n=105	600 µgm n=237	p-value
Mild to severe nausea	9 (9%)	23 (22%)	40 (17%)	0.05
Mild to severe vomiting	7 (7%)	13 (12%)	19 (8%)	0.36
Mild to severe diarrhoea	0	1 (1%)	7 (3%)	0.49*
Mild to severe dizziness	10 (10%)	19 (18%)	38 (16%)	0.30
Mild to severe shivering	42 (41%)	71 (62%)	148 (62%)	<0.001

* Generalised Fisher exact test

Table 3.2.7. Adjusted comparison of the outcome and side effects of the three dosage groups of oral misoprostol

	400μgm/500 μgm	400μgm/600 μgm	p-value
Estimated ratio (95%CI) of % with blood loss ≥ 500 mL	2.67 (1.10 – 6.46)	1.75 (0.67 – 4.57)	0.09
Estimated ratio (95%CI) of % with repeat syntometrine injection	3.88 (1.56 – 9.69)	3.30 (1.19 – 9.13)	0.006
Estimated ratio (95%CI) of geometric mean of blood loss	1.23 (1.08 – 1.40)	1.25 (1.10 – 1.43)	<0.001
Estimated ratio (95%CI) of % with geometric mean of third stage	1.10 (0.96 - 1.25)	1.10 (0.97 - 1.25)	0.22
Estimated ratio (95%CI) of % with mild to severe vomiting	0.44 (0.16 – 1.20)	1.10 (0.48 – 2.51)	0.19
Estimated ratio (95%CI) of % with mild to severe dizziness	0.69 (0.31 – 1.54)	1.34 (0.69 – 2.60)	0.33
Estimated ratio (95%CI) of % with mild to severe nausea	0.55 (0.24 – 1.26)	1.71 (0.91 – 3.22)	0.034
Estimated ratio (95%CI) of % with mild to severe shivering	0.33 (0.20 – 0.56)	1.04 (0.61 – 1.75)	<0.001

Appendix A: Data collection form, including patient information sheet, consent form, and information to doctors and midwives

The third stage study

Department of Obstetrics and Gynaecology

UCL

1995

Contents:

Information for doctors and midwives

Patient information sheet

Consent form	→ To be kept in patient's notes.
Data collection form	→ To be kept in data box in labour ward computer room
Self-filling questionnaire	→ To be kept in data box in labour ward computer room

Information for Doctors and Midwifery Staff
The Third stage study

The aim of this information sheet is to try to answer possible questions in relation to this study

- Misoprostol is a widely used drug with a well known safety record in the field of peptic ulcer disease.
- Its trade name is Cytotec. More information is available about the drug in the BNF in the section entitled 'Ulcer healing agents' (page 20-30 depending on the edition). It is also present in another form called Arthrotec. This is a combination of Diclofenac and Misoprostol.
- Prostaglandins administered parenterally are known to be effective in treating intractable post partum haemorrhage. Misoprostol is a Prostaglandin E1 analogue in tablet form.
- The absorption of misoprostol is very quick. It reaches its peak level in the circulation within minutes. *See graph in labour ward.*
- The aim of this study is to see whether misoprostol can be as effective as syntometrine. Unlike syntometrine, misoprostol does not seem to increase the blood pressure, and does not cause vomiting.

What you need to do is

- Exclude contraindications

1. Placenta Praevia
2. Multiple pregnancy
3. Intrauterine death
4. < 32 weeks gestation
5. Previous PPH
6. Anaemia < 10 gm/dl and MCV < 75
7. Parity > 5
8. Preeclampsia
9. Any other circumstances where the clinician in charge feels that there are overwhelming contraindications to involvement in the study.

- Speak to patient
- Consent
- Deliver the baby, clamp and divide the cord, and immediately give patient 400 μgm misoprostol (2 tablets) by mouth. Placenta is to be delivered by controlled cord traction as usual. The action of misoprostol seems to be a little faster than that of syntometrine.
- The dosage administered should be documented in the patients drug cardex
- Midwife is to fill data collection form
- Ensure that data collection form and *patients questionnaire* are set aside for collection
- Misoprostol is available in the labour ward

Patient Information Sheet

The Third stage study

At the Obstetric (maternity) hospital we are always looking for ways of improving the care we give to mothers and to their babies.

One area which we are looking into at the moment is the way in which the afterbirth (placenta) is delivered. The time during birth when this happens is called the third stage of labour. In the Obstetric Hospital you would usually receive an injection as your baby is born, then the umbilical cord joining the baby to the afterbirth is clamped and cut. You might push out the afterbirth yourself or sometimes the midwife uses the cord to help bring the afterbirth out. The injection is given, as we believe that it helps the womb to contract (get smaller) and that it reduces the amount of blood loss after delivery.

Unfortunately the injection can have side effects: It is known to increase the blood pressure it can cause a feeling of sickness. In this country disposable clean needles are used all the time, in other parts of the world this may not be possible, and therefore it can transmit disease.

Recently it has been discovered that tablets (made from a substance called prostaglandin) that have been widely and safely used to treat stomach ulcer disease can bring about contraction of the womb. These tablets are given by mouth. We have good reason to believe that they are as good as the injection. Furthermore, these tablets are known to have no effect on blood pressure. Unlike the injection, they are not affected by high temperatures, and this makes them invaluable in other parts of the world. The aim of our study is to see whether these tablets really work and to assess their side effects.

If you agree to join the study this is what will happen: After the delivery of your baby and clamping of the cord, you will be asked to swallow two small tablets. You and the midwife looking after you will be asked to fill in a questionnaire about your experience with the treatment and any side effects. We know from experience with the tablets in stomach ulcer disease that side effects are not common, and if they happen, rarely require any treatment.

You do not have to take part in the study if you do not want to. If you decide to take part you may withdraw at any time without having to give a reason. Your decision whether to take part or not will not affect your care and management in any way.

Thank you for your help

Consent Form

Third stage study

Have you read the information sheet about this study Yes/No

Have you had the opportunity to ask questions and discuss study Yes/No

Have you received satisfactory answers to all your questions? Yes/No

Have you received enough information about this study? Yes/No

Which doctor have you spoken to about this study? Dr----------

Do you understand that you are free to withdraw from this study

i) at any time Yes/No

ii) without giving a reason for withdrawing Yes/No

Do you agree to take part in this study?

Signed.....Date.....

Name in block letters.....

Doctor/Midwife.....
Signed.....

To be filled by midwife

Affix a sticker or write	Date	Midwife name	
Patient name	Age	Parity	Gestation
Unit number	Last Hb level and date		
Last recorded weight	Height		

Did your patient receive Misoprostol or Syntometrine? Misoprostol Dose: 400 / 500 / 600 mcg
Syntometrine

Features of labour

Please write the length of first and second stages: First.....Second.....

Did your patient have the following:

Prostin pessaries	Yes/No
Syntocinon augmentation	Yes/No
Epidural anaesthesia	Yes/No
Narcotic analgesia	Yes/No
Anti emetic injections	Yes/No

Features of delivery

A *Baby:*

SVD without Episiotomy — Baby's weight
SVD + Episiotomy
Ventouse without episiotomy
Ventouse + Episiotomy
Forceps
Kielland forceps
Caesarean section

Tears — First degree — Second — Third

B *Placenta:*
Length of third stage (CCT)
Estimated blood loss
Manual removal of placenta

C *Blood pressure*
Last measured BP prior to delivery
BP one hour after delivery

D *Temperature*
Last measured temperature prior to delivery
Temperature one hour after delivery
Temperature prior to discharge to the ward

E Did your patient vomit within one hour of receiving the tablet?

F If 'Yes' to E, did she vomit during labour i.e. before misoprostol Yes/No

G Do you think that your patient swallowed the tablets easily? Yes/No

---

Did your patient need further ⇒ Syntometrine / Syntocinon infusion / Ergometrine

---

When do you think the uterus contracted after delivery (minutes)

Do you think the uterus contracted *faster* *slower* or *similar* to syntometrine

Was the uterus well contracted one hour after delivery 0 1 2 3 4
(0=Poorly contracted 4=very strongly contracted)

Did your patient require any analgesia for 'after-pains' Yes/No

Specify →.....

Which postnatal ward was the patient discharged to ?
Did the patient fill the Questionnaire?

Appendix 3.B: Patients' Questionnaire:

To be filled in by the patient one hour after delivery

Patient details: *(Affix a sticker or write)*

Please write your name Date Time

To what extent, if at all, you have experienced the following symptoms since you have delivered today? For each symptom please circle the number which best describes the extent to which you have experienced that symptom. Even if none of the numbers seem exactly right to you choose the one that is closest to your experience. Please be sure to circle the one number for each symptom. Remember we are only interested in your experience as you see it, so there are no 'right' or 'wrong' answers.

I have experienced this		0 = not at all 1= mildly 2= moderately 3= quite strongly 4= very strongly				
1	Nausea	0	1	2	3	4
2	Headache	0	1	2	3	4
3	Hot flushes	0	1	2	3	4
4	Dizziness	0	1	2	3	4
5	Vomiting	0	1	2	3	4
6	Tiredness	0	1	2	3	4
7	Diarrhoea	0	1	2	3	4
8	Abdominal pain	0	1	2	3	4
9	Shivering	0	1	2	3	4

Please attach to the front of patients notes if completed
Or put in collection box, please ensure that patient name is completed

Chapter 4

A randomised controlled trial examining the efficacy and side effects of oral Misoprostol versus other oxytocics in active management of the third stage of labour.

Background

Active management of the third stage of labour is the main strategy implemented to reduce postpartum bleeding. Drugs used for prophylaxis against PPH include oxytocin, ergometrine, and Syntometrine. The most widely used policy in the UK and most of the former British commonwealth countries for active management of the third stage of labour involves the administration of syntometrine, unless the patient is hypertensive where she receives syntocinon, or if the patient has a previous history of PPH, then she would receive ergometrine.

The main problems arising through the use of syntometrine in third stage management are its associated side effects. Its gastrointestinal side effects, in the form of nausea and vomiting, make it quite unpopular among women. Syntometrine is also known to produce headache and causes a rise in blood pressure in normotensive women, and is therefore contraindicated where there is hypertension in pregnancy. Furthermore, it's parenteral administration, instability at high temperatures, and special storage requirements hinder its widespread use over the world (Prendiville & Elbourne, 1989; Data sheet compendium, 1993).

Prostaglandins possess strong uterotonic features, are highly effective in the management of intractable PPH (Toppozada *et al.*, 1981), and are not hypertensive (Prendiville & Elbourne 1989), therefore they may be superior to syntometrine in prophylactic management of the third stage of labour. The known advantages of Misoprostol, its potent uterotonicity, rapid absorption and equally rapid effect (Gaud & Connors, 1992), which has also been demonstrated on the postpartum uterus (Choo *et al.*, 1998), the possibility of its oral administration, in addition to its advantage of not causing a rise in blood pressure for doses up to

800 μgms (Brecht, 1987), make it appear as an ideal agent for prophylaxis against PPH in the third stage of labour. Results of the two pilot studies (chapter 3) suggest that Misoprostol may act as an alternative to conventional injectable uterotonics used in the management of the third stage of labour and prevention of PPH in low risk women. At this stage, a randomised-controlled trial was needed.

We decided to investigate the efficacy and side effects of oral misoprostol in comparison with the established practice of prophylactic management of the third stage of labour in the U.K. Its main objective was to investigate whether active management of the third stage of labour could be carried out safely with oral misoprostol, and to determine whether, in terms of maternal morbidity, it is justifiable to use misoprostol in place of the current policy that involves using syntometrine, syntocinon, or ergometrine. The hypothesis being that oral misoprostol, as a potent uterotonic agent, that does not have the hypertensive properties and the gastrointestinal side effects of syntometrine, may take the place of currently used injectable oxytocics in the routine prophylactic management of the third stage of labour.

Patients and methods

The randomised controlled trial was carried out between April 1996 and March 1998 at The Obstetric Hospital, U.C.H, which has an annual birth rate of just over 2500. The study protocol was reviewed and approved by the local Ethics Committee.

Pharmacological management of the third stage of labour usually involves the routine use of intramuscular syntometrine. However, due to the hypertensive properties of syntometrine, women with pregnancy-induced hypertension and those with cardiac disease are usually given 10 units of intramuscular syntocinon. Women at high risk of PPH, e.g. women of high parity (4 or more), or with a history of atonic PPH, are usually given 500 μgm of intravenous ergometrine, which is considered more potent than intramuscular syntometrine or syntocinon.

The primary aim of this randomised trial was to ascertain whether the use of 500 μgm of oral misoprostol could replace this policy, without an increase in the incidence of PPH. The secondary aim was to assess the frequency and severity of the side effects of both policies, as perceived by patients.

Pregnant women were eligible to take part in this study if they were expected to have a vaginal delivery at the hospital. The three exclusion criteria were planned caesarean section, history of severe bronchial asthma (requiring hospital admission and the use of steroids), and having a water birth. Specifically, a history of antepartum haemorrhage after 20 weeks, previous PPH, anaemia (haemoglobin concentration < 10 g/dL), non-cephalic presentation, multiple pregnancy or cardiac disease were not considered to be exclusion criteria.

Information sheets explaining the aims of the study were distributed to potential participants in antenatal classes, antenatal clinics, and the Day Assessment Area. On admission to labour ward, women were reminded of the study, and a Written Informed Consent Form was obtained if they still wished to participate.

When vaginal delivery was imminent, the midwife picked a randomisation envelope from a batch previously prepared by means of computer generated, blocked randomisation tables with varying block size. The opaque, sequentially numbered sealed envelopes were stored in the labour ward central station, and indicated the method of third stage management to which the patient was allocated. Each envelope contained a folded card with one of two sets of instructions; those marked with **"M"** indicated randomisation to receive 500 μgm of orally administered misoprostol tablets immediately after delivery of the baby and clamping and division of the cord. Cards marked with **"O"** indicated randomisation to the standard policy of "other oxytocic agents" i.e. syntometrine, syntocinon, or ergometrine, depending on maternal condition, one of which was administered after delivery of the anterior shoulder. The choice of which of these three agents to use was made by the midwife caring for each individual patient, following standard guidelines: a woman randomised in the "**O**" group received syntometrine, unless she was hypertensive, in which case she received 10 IU of syntocinon intramuscularly (IM). Grand multiparous women (para 4 or more), who were not hypertensive or had previous history of PPH, received 500 μgm of ergometrine intravenously (IV). In both arms of the trial, the placenta was delivered by controlled cord traction.

The data collection form was completed by the midwife caring for each patient. This form contained information on maternal characteristics such as age, parity, height, weight, gestation at delivery, and obstetric history, including history of PPH, essential or pregnancy induced hypertension (defined as diastolic blood pressure ≥ 100 mm.Hg or systolic blood pressure ≥ 150 mm.Hg). Labour variables recorded included information on whether it was induced, or augmented with syntocinon, whether the mother received epidural analgesia, narcotic

analgesia, and antiemetics, whether the mother was nauseous in labour, whether she vomited (and, if so, the frequency), whether she felt cold and shivery, and her temperature in labour. Delivery variables included information on the mode of delivery, whether episiotomy was performed, and the occurrence of genital tears.

In the United Kingdom, recording of the amount of blood loss immediately after delivery is a pre-requisite prior to completion of the birth register. Blood loss is subjectively estimated by the attendant midwife or obstetrician. In line with other landmark papers that have investigated the management of the third stage of labour (Nieminen & Jarvinen, 1963; Dumoulin, 1981; Prendiville *et al.*, 1988; Begley, 1990; McDonald *et al.*, 1993; Mitchell & Elbourne, 1993; Khan *et al.*, 1995; Yuen *et al.*, 1995), we also employed clinical assessment of blood loss. Because this assessment is subjective, surrogate and objective indices of blood loss were also recorded, including the need for blood transfusion, use of other therapeutic oxytocics, length of the third stage, and whether manual removal of the placenta was performed. We also attempted to record changes in haemoglobin and haematocrit concentration before and after delivery. Ideally, we aimed to obtain a prenatal blood sample from all women during labour, for accurate comparison with a postnatal blood sample one day after delivery. However, since this is not part of the normal clinical practice in the UK, a large proportion of patients (nearly 55% in the randomised trial) declined these blood tests, or had been discharged earlier (see discussion). Blood loss during delivery and prior to leaving the labour ward was recorded. Any delayed haemorrhage within the first 24 hours was also documented. All of the above constitute the main outcome measures of the studies included in the third stage reviews of The Cochrane Library (McDonald *et al.*, 1998; Prendiville *et al.*, 1998).

Other third stage variables included information on cord management, the length of the third stage, incidence of manual removal of the placenta, whether further oxytocic administration was needed, and the need for transfusion of blood or blood products. Further information was obtained on vital signs (blood pressure and temperature) measured before (within one hour prior to delivery), and after administration of the trial treatment (soon after delivery, then 30 and 60 min. later). It was also recorded whether the patient vomited after receiving the drug, and whether she received analgesics for after-pains. One day after delivery, a sample of venous blood was obtained from each woman, for measurement of haemoglobin concentration and haematocrit, to be compared with a previous sample obtained in labour or late in pregnancy (if done within 2 weeks of delivery). Other end points were also considered, such as severe PPH (≥ 1000 mL), secondary PPH (occurring after 24 hours), and the need for subsequent evacuation of retained products of conception.

The main secondary end points of this study were to estimate the incidence and severity of side effects. Women were therefore requested to complete a questionnaire after delivery, before leaving the labour ward. This questionnaire recorded women's perception of side effects such as nausea, vomiting, abdominal pain, diarrhoea, hot flushes, headache, tiredness, dizziness, and shivering. The severity of each symptom was rated from 0 (none) to 4 (very severe).

Statistical methods

In the literature, the rate of PPH when using standard oxytocics varies between 5% to 18% (Prendiville *et al.*, 1988; McDonald *et al.*, 1998). In the first pilot

study, the rate of PPH associated with the use of a 600 μgm oral misoprostol dosage was 6%. We therefore assumed that the rate of PPH in our hospital when using standard oxytocics would be about 5%, and judged that a two-fold increase in this rate would be clinically unacceptable. We therefore based our study on a sample size of one thousand women, which would allow us to detect such a difference in the incidence of PPH (from 5% to 10%), with a power of 80% at the two-sided 5% significance level (Casagrande *et al.*, 1978).

Statistical analysis was performed using SPSS for windows. Data for categorical variables are presented as numbers and percentages, and associations were assessed using the chi-squared test or Fishers exact test, as appropriate. Relative risk estimates between the misoprostol and "other oxytocics" arm, and their corresponding 95% confidence intervals (CI) were calculated for the PPH rate, and rates of side effects. Data for continuous variables are presented as means and standard deviations (SD) if they were normally distributed; otherwise medians and interquartile ranges (25^{th} - 75^{th} percentile) are presented. Comparisons of means between the two randomised arms were conducted with the Students *t*-test, and comparisons of medians were conducted using the Mann-Whitney test. Changes in certain continuous variables such as systolic and diastolic blood pressure, temperature, haemoglobin and haematocrit concentrations before and after administration of the trial drug were assessed by the paired sample t-test. All tests were two-tailed and the significance level was set at 5%.

Statistical comparisons were performed only between the two randomised arms. No statistical comparisons were made between the misoprostol arm and the three groups that make up the "other oxytocics" treatment arm, since this would constitute non-randomised comparisons of incomparable groups. However, for the

sake of completeness, summary statistics are presented, not only for the two randomised arms, but also for the three groups that make up the "other oxytocics" arm.

Results

The total population included in this study were 1000 randomised women. 501 were randomised and received 500 μgm of Misoprostol orally, and 499 were randomised and received "other oxytocics". 401 (80%) of the "other oxytocics" arm received Syntometrine, 89 (18%) received Syntocinon, and 9 (2%) received ergometrine.

Table 4.1 demonstrates the baseline characteristics and obstetric history of the 1000 randomised patients by study group. Both randomised groups were comparable at entry into the study. The studied population included seven twin pregnancies, four of whom were randomised to misoprostol, and three to the "other oxytocics" arm. There were three patients with heart disease and two with fibroid uterus, out of whom two and one were randomised to the misoprostol arm, respectively.

Table 4.2 represents a comparison between the randomised arms of events during the first and second stages of labour, i.e. before administration of the trial treatment. There were no statistically significant differences in labour events or length of labour between the two arms. The number of women experiencing nausea and vomiting in labour was slightly higher in the misoprostol arm, but this difference was not statistically significant (33% and 20% compared to 31% and

18% respectively). The number of mothers receiving epidural analgesia in labour was similar in both arms (44% in the misoprostol arm versus 46% in the "other oxytocics" arm, p-value = 0.55).

Table 4.3 represents a comparison of delivery variables between the studied arms before administration of the trial treatment. There were no significant differences in method of delivery, presence of tears, analgesic administration, or cord management between the two arms. However, it is clear from these two tables that the three groups; namely the syntometrine, syntocinon, and ergometrine, which make up the "other oxytocics" arm were not individually comparable, neither to one another, nor to the misoprostol group. The syntometrine group, for example, which included mostly low risk women, had a higher rate of spontaneous vaginal deliveries, a lower rate of syntocinon augmentation, and shortest length of the second stage of labour.

Table 4.4 describes the effects of the trial treatments on the third stage of labour. The rate of PPH (blood loss ≥ 500 mL) was 12% in the misoprostol arm. In the group allocated to the "other oxytocics" arm, the PPH rate was 11%, which was more than double the estimate used in the power calculation (see discussion). No significant difference was found between the two groups (RR 1.10, 95% CI of 0.79 to 1.55, p-value = 0.76). The rate of severe PPH (blood loss ≥ 1000 mL) was also similar (1.8% in the misoprostol arm, and 2.0% in the "other oxytocics" arm (RR 0.9, 95% CI of 0.37 to 2.19). The median blood loss in both randomised arms was 250 mL. The proportions of women requiring manual removal of the placenta and blood transfusion, and the length of the third stage of labour were all comparable between the two randomised arms. The percentage of women requiring further oxytocic administration was slightly higher in the misoprostol

arm (14% compared to 10% in the "other oxytocics" arm), but this difference was not statistically significant (p-value = 0.08). Among the "other oxytocics" arm, the syntometrine group, which included fewer hypertensive women and a higher proportion of normal deliveries, had the lowest rate of PPH (9%). In contrast, the syntocinon group, which included more hypertensive women and a lower proportion of normal deliveries, had a markedly higher rate of PPH and severe PPH (23%). One woman in each randomised arm developed secondary PPH. Evacuation of retained products of conception (ERPC) was performed in each case.

Table 4.5 represents a comparison of the changes in vital signs after administration of the trial treatment between the two randomised arms. There was a statistically significant increase in mean temperature of about 0.6°C in the misoprostol arm, in comparison to an increase of only 0.3°C in the "other oxytocics" arm. This difference of 0.3°C was statistically significant (95% CI of 0.26 to 0.42, p-value < 0.001). 4.9% of women in the misoprostol arm experienced a rise in temperature of > 2°C, compared with only 0.2% in the "other oxytocics" arm; this difference was statistically significant (p-value < 0.001). Three women in the study had a rise in temperature of 4°C; all of whom were in the misoprostol arm.

There was a slight fall in systolic blood pressure in the misoprostol arm (mean change of –1.3 mm.Hg) in comparison to a small increase in the "other oxytocics" arm (mean change of +0.1 mm.Hg). The difference between both arms was not statistically significant (p-value = 0.09). Both arms showed a comparable small reduction in diastolic blood pressure, haemoglobin concentration and haematocrit levels.

Table 4.6 summarises the patients' reported side effects. In the misoprostol arm, 445 (88%) of the women returned a completed side effect form, compared to 401 (80%) in the "other oxytocics" arm (p-value = 0.003). Among these women, nausea, headache, dizziness, and tiredness were reported more often in the "other oxytocics" arm, and these differences were statistically significant. There were no differences in the reported incidence of vomiting, hot flushes, abdominal pain, or diarrhoea between the two arms. The most prominent side effect for misoprostol was shivering, which occurred twice as often in the misoprostol arm, compared to the "other oxytocics" arm. This difference was statistically significant; 72% compared to 37% (RR 1.95, 95% CI of 1.69 to 2.25, p-value < 0.001). Among the misoprostol group, shivering occurred significantly more often among women who had received epidural analgesia (230 out of 384 women, or 60%), than in those who had not (236 out of 462 women, or 51%), p-value = 0.01. However, no interaction was found between the effect of misoprostol on shivering and whether epidural analgesia was given (interaction test p-value = 0.38). The shivering rate was twice as high in the misoprostol arm as in the "other oxytocics" arm for both subgroups of patients i.e. those who had or did not have epidural analgesia (Table 4.7).

Another side effect that was noted in the misoprostol arm was pyrexia (temperature above 37.5°C), which was seen in 114 women or 22.8% (RR 2.47, 95% CI of 1.81 to 3.37, p-value < 0.001). The high shivering rate was associated with a significantly high incidence of pyrexia, such that 27.5% of those who shivered developed pyrexia, compared to 10.0% among non-shiverers (p-value < 0.001). When temperature was measured prior to discharge of the patients from the labour ward, over two hours after delivery, it was still significantly elevated among shiverers in the misoprostol arm (23.1% compared to 7.8%, p-value <

0.001). However, the rate of pyrexia among non-shiverers in the misoprostol arm was 7.8%, which was comparable to that among women receiving "other oxytocics", whether they had shivered or not (6.0% and 5.8% respectively, p-value = 1.0). A clear association was found between shivering and the rise in temperature in the misoprostol arm (difference in mean change in temperature between shivering and non-shivering patients in the misoprostol group = 0.38°C, 95% CI of 0.24 to 0.52), but not in the "other oxytocics" arm (difference in mean change in temperature between shivering and non-shivering patients in the "other oxytocics" arm = 0.04°C, 95% CI of -0.09 to 0.17) (F-test of interaction between shivering and randomised group on the change in temperature = 12.4, p-value < 0.001).

Table 4.8 demonstrates the severity of reported side effects for women in each arm. Shivering was the only reported side effect that was significantly higher in the misoprostol arm.

Discussion

In this randomised study, orally administered misoprostol was found to be as effective as injectable oxytocics in terms of the incidence of PPH and blood loss during and after delivery. This confirms the findings of the two observational studies (chapter 3), and suggests that a policy using oral misoprostol is a safe and simple alternative to the current policies that use injectable oxytocics. The current widely practiced policy of using ergometrine-containing preparations in the third stage of labour requires the division of women into groups, according to their pre-existing risk factors. Women in different groups are then given different

oxytocics, a process susceptible to human error; such error can lead to serious morbidity and occasionally even death (DHSS, 1996; Ringrose, 1962). Oral misoprostol, on the other hand can safely be given to women in all of these categories, thus simplifying the management of the third stage. In this study, women not randomised to receive misoprostol had to be prescribed one of the three different agents in order to achieve the same therapeutic goal.

In the pilot studies (Chapter 3), the lower PPH rates associated with the use of oral misoprostol (6% with the 600 μgm dosage, and 8% with the 500 μgm dosage) may be explained by the inclusion of only low risk women, and exclusion of high risk cases, from both pilot studies. In the randomised controlled trial the results in the misoprostol arm with regards to blood loss variables are all the more impressive, given that this group included both high and low risk women.

It is worth noticing, however, that the PPH rate of 11% in the "other oxytocics" arm was higher than our estimate which was used for power calculation. This could be explained firstly by variation between the PPH rate in our hospital in comparison to other studies, to the inclusion of both low and high risk patients, and finally to the possibility of increased awareness of blood loss associated with the implementation of the randomised controlled study. In a blinded trial one would be reassured that this extra attention would be similar in both arms. However, although this trial was not blinded, the use of other objective measures of blood loss such as the frequency of blood transfusion, and the mean change in haemoglobin concentration before and after delivery supported the finding of a non-significant difference between the two groups.

Misoprostol was better tolerated than the "other oxytocics" in terms of the incidence of nausea, headache, and dizziness, although the difference in the incidence of other gastrointestinal side effects was not statistically significant. These side effects are an important factor in reducing the acceptability of ergometrine-containing preparations, and have been a major stimulus to clinicians to search for an alternative over the past three decades (McDonald *et al.*, 1993; Dwyer, 1994). In this trial, we relied on patient perception and self-reporting of side effects. It is important to highlight that there is a potential bias inherent in this comparison between the two arms of the trial, because of the differential rate of return of the side effect forms. It is unlikely, however, that this potential bias could account for the sizeable differences between the two arms in the incidence of some of the side effects, such as headache, and shivering (Table 4.6).

Shivering and rise in temperature were the main side effects of misoprostol, and there was a clear association between both side effects. In the misoprostol arm, women who reported shivering had a mean rise in temperature of 0.38°C over non-shiverers; however shivering women in the "other oxytocics" arm did not exhibit a significant increase in their temperature in comparison to non-shivering women. Whilst the mean rise in temperature in the misoprostol arm was about 0.6°C, the highest recorded temperature in our sample was 40°C.

Temperature rise is a well-recognised side effect of prostaglandins (Milton & Wendlandt, 1971; Veale & Cooper, 1975; Jain & Mishell, 1994; Haberal *et al.*, 1996; Creinin *et al.*, 1997 a, b; Srisomboon *et al.*, 1997 a). The mechanism by which prostaglandins increase heat production, however, is still unclear. None of the women in our study were prescribed any treatment. In spite of this knowledge, we feel that a rise in temperature after delivery often stimulates health

professionals to initiate investigations and treatment for other possible causes of pyrexia. In some parts of the world, this might well lead to the prescription of anti-malarials, or antibiotics for the treatment of presumed chorio-amnionitis.

Studies that have investigated the use of oral misoprostol in the treatment of peptic ulcer have not reported shivering and rise in temperature as side effects to the drug. Reported side effects to the use of oral misoprostol (400 to 800 ugm/day in divided doses) in the treatment of duodenal ulcer or in osteoarthritis and rheumatoid arthritis patients using Arthrotec (a combination of 50 mg of diclofenac and 200 ugm of misoprostol) were mainly gastrointestinal in nature, usually occurring upon initiation of therapy. Abdominal pain is the most frequently reported side effect, followed by mild self-limiting diarrhoea, nausea, dyspepsia, falatulence, vomiting, and constipation. The most frequent nongastrointestinal side effects reported are headache and dizziness (Dajani *et al.*, 1991; Lanza *et al.*,1991; Geis, 1992; Numo, 1992; Gagnier, 1993; Melo Gomes *et al.*, 1993). However, the only report on the pyrogenic effect of misoprostol in peptic ulcer was that by Baulieu *et al.* (1992) where recurrent bouts of pyrexia occurred in response to misoprostol administration in a cirrhotic patient.

In the field of obstetrics, the incidence of fever in association with misoprostol has been reported in various studies, and has been contributed to the direct effect of the drug. Haberal *et al.* (1996) reported fever as a side effect to oral misoprostol in early abortion induction, along with nausea, vomiting, diarrhea, hypotension, headache and abdominal pain. Creinin *et al.* (1997 b) reported a subjective sensation of fever and chills after misoprostol administration in 31% of their study subjects while investigating the efficacy of oral methotrexate and vaginal misoprostol for medical abortion. Jain and Mishell (1994) reported that

pyrexia was the highest noted side effect to misoprostol when used for mid-trimester termination of pregnancy, occurring in 63% of women receiving misoprostol (200 μgm intravaginally every 12 hours), compared to only 11% among women receiving dinoprostone (20 mg intravaginally every 3 hrs.), (p-value < 0.001).

However, shivering was not known to be a side effect to misoprostol prior to using it in the third stage of labour. The use of single oral misoprostol doses of up to 800 μgm (Schaff et al., 1996; Creinin et al., 1997 a, b), and total daily doses up to 2200 μgm (El-Refaey & Templeton, 1995), was not associated with this side effect.

Shivering occurred twice as often in the misoprostol arm, and was also significantly more severe than in the "other oxytocics" arm. It was self-limiting, tended to occur within 5 to 10 minutes of drug administration, and lasted about 20 to 30 minutes. However, it was felt that this common side-effect may reduce the acceptability of the drug, since a small number of women in our study commented that shivering interfered with their ability to hold and feed the baby immediately after delivery.

Whilst shivering is known to be a side effect of epidural analgesia (Buggy & Gardiner, 1995; Jaameri *et al.*, 1996), this study shows that shivering is a genuine side effect of misoprostol. There are indications from unpublished data, and one published report that shivering might be dose-dependant (Hofmeyr *et al.*, 1998). Further research is therefore needed to understand the interplay between pyrexia and shivering, and to identify methods to overcome these side effects. During the course of this randomised trial, it was decided to further investigate into the

occurrence of shivering and pyrexia after oral misoprostol administration in a sub-set of women in each arm, the results of which will be discussed in chapter 5.

Although further oxytocics were used more often in the misoprostol group, 13.6% compared with 10.0% in the "other oxytocics" group, this was not statistically significant. Other factors may have contributed to this result. Since misoprostol is a comparatively new drug, and has not been widely used in third stage management, this may have resulted in a lack of confidence in the drug by the midwives. In addition there is a rapid turnover and change of staff in this hospital, which necessitated frequent teaching of the staff about misoprostol.

A possible source of bias in this randomised trial lies in the fact that it was not blind, since, unfortunately, the manufacture and use of specifically formulated tablets was not possible. Another issue is the method of assessing postpartum blood loss, which was visually estimated.

The lack of an enterally administered thermostable agent for prevention of PPH in both the developing and developed world is a major weakness in the fight against maternal mortality (Nazerali & Hogerzeil, 1998). This study proves that misoprostol is comparable in efficacy to other oxytocics for the management of the third stage of labour. It has proved that misoprostol does not cause an increase in blood pressure, has few side effects (mainly shivering), and is well tolerated. These findings suggest that Misoprostol may be used in the routine management of the third stage of labour. It has great potential to reduce maternal mortality due to PPH and is comparable in its efficacy to other commonly used oxytocics.

Table 4.1. Baseline characteristics of the studied groups

Mean (SD) of:	Misoprostol n = 501	Other n = 499	Other Oxytocics			* p-value
			Syntometrine n = 401	Syntocinon n = 89	Ergometrine n = 9	
Maternal age (yrs.)	30 (5.8)	30 (6.0)	29 (6.0)	30 (6.3)	33 (6.0)	0.20
Height (cm)[1]	163 (8.0)	164 (6.8)	164 (6.9)	166 (6.6)	164 (5.8)	0.16
Maternal weight (kg)[2]	76 (13.6)	76 (12.5)	75 (11.5)	81 (15.1)	79 (19.7)	0.81
Systolic BP (mm.Hg)[3]	118 (13.1)	119 (13.6)	116 (11.2)	130 (16.9)	124 (15.8)	0.29
Diastolic BP (mm.Hg)[3]	74 (9.7)	74 (9.9)	75 (11.5)	81 (15.1)	79 (19.7)	0.62
Gestational age (wks)	40 (1.3)	39 (1.9)	39 (1.9)	39 (1.9)	40 (0.9)	0.16
Haemoglobin (g/dL)[4]	11.6 (1.1)	11.5 (1.1)	11.5 (1.1)	11.5 (1.2)	11.0 (2.0)	0.40
Haematocrit (%)[4]	0.35 (0.03)	0.35 (0.04)	0.35 (0.03)	0.35 (0.04)	0.34 (0.06)	0.36
Parity:						
No. (%) Primiparous	236 (47)	255 (51)	201 (50)	54 (61)	-	0.19
No. (%) Para 1 - 3	242 (48)	230 (46)	197 (49)	29 (33)	4 (44)	
No. (%) Parity ≥4	23 (5)	14 (3)	3 (1)	6** (7)	5 (56)	
No. (%) previous PPH	21(4)	19 (4)	15+ (4)	2** (2)	2 (22)	0.76

1. n = 430 in the misoprostol arm, and n = 412 in the "other oxytocics" arm
2. n = 393 in the misoprostol arm, and n = 357 in the "other oxytocics" arm
3. n = 497 in the misoprostol arm, and n = 493 in the "other oxytocics" arm
4. n = 303 in the misoprostol arm, and n = 314 in the "other oxytocics" arm

* P-value comparing the two randomised arms, i.e. misoprostol and overall "other oxytocic" arms

SD = Standard deviation

** These were also women with high blood pressure

\+ These were women who had previous PPH due to an instrumental delivery

Table 4.2. A comparison of events in labour between the studied groups

	Misoprostol n = 501	Other n = 499	Other Oxytocics			*p-value
			Syntometrine n = 401	Syntocinon n = 89	Ergometrine n = 9	
No. (%) induction of labour	122 (24)	142 (29)	104 (26)	36 (40)	2 (22)	0.14
No. (%) syntocinon augmented	168 (34)	155 (31)	107 (27)	46 (52)	2 (22)	0.43
No. (%) narcotic analgesia	201 (40)	195 (39)	157 (39)	34 (38)	4 (44)	0.76
No. (%) epidural analgesia	219 (44)	227 (46)	173 (43)	53 (60)	1 (11)	0.55
No. (%) antiemetic administered	186 (37)	186 (37)	107 (27)	46 (52)	2 (22)	0.94
No. (%) nausea in labour	165 (33)	152 (31)	129 (32)	23 (26)	-	0.40
No. (%) vomited in labour	101 (20)	91 (18)	75 (19)	16 (18)	-	0.44
No. (%) cold & shivery in labour	78 (16)	67 (14)	57 (14)	10 (11)	-	0.34
Median (IQR) length of first stage (hours)[1]	6.2 (4 - 9)	6.3 (4 - 10)	6.2 (4-10)	7.0 (4-10)	7.0 (5-9)	0.84
Median (IQR) length of second stage (mins.)[1]	42 (17-106)	40 (15-103)	36 (15-100)	63 (23-119)	30 (8-82)	0.48

1. n = 487 in the misoprostol arm, and n = 487 in the "other oxytocics" arm.

* P-value comparing the two randomised arms, i.e. misoprostol and overall "other oxytocics" arms

IQR = inter-quartile range

SVD= Spontaneous vaginal delivery

Table 4.3. A comparison of delivery variables between the studied groups

	Misoprostol n = 501	Other n = 499	Other Oxytocics			*p-value
			Syntometrine n = 401	Syntocinon n = 89	Ergometrine n = 9	
No. (%) with SVD	387 (77)	390 (78)	323 (80)	60 (67)	7 (78)	0.22
with ventouse	87 (17)	72 (14)	47 (12)	23 (26)	2 (22)	
with forceps	27 (5)	37 (7)	31 (8)	6 (7)	-	
No. (%) with episiotomy	111 (22)	120 (24)	87 (22)	32 (36)	1 (11)	0.48
No. (%) with vaginal tears	230 (46)	221 (45)	184 (46)	33 (37)	4 (44)	0.59
No. (%) with afterpain analgesia	123 (25)	118 (24)	92 (23)	24 (27)	2 (22)	0.78
No. (%) cord management:						
with no cord traction	8 (2)	8 (2)	5 (1)	3 (3)	-	0.15
traction within 30 seconds	13 (3)	14 (3)	13 (3)	1 (1)	-	
traction before signs of separatn.	66 (13)	43 (9)	36 (9)	6 (7)	1 (11)	
traction after signs of separation	413 (83)	433 (87)	346 (87)	79 (89)	8 (89)	
Mean (SD) birthweight (kg)	3418 (474)	3373 (525)	3366 (531)	3377 (492)	3652 (542)	0.16

* P-value comparing the two randomised arms, i.e. misoprostol and overall "other oxytocic" arms

SD = Standard deviation

Table 4.4. The effects of the trial treatments on the third stage of labour between the studied groups

	Misoprostol n = 501	Other n = 499	Other Oxytocics			*p-value
			Syntometrine n = 401	Syntocinon n = 89	Ergometrine n = 9	
No. (%) blood loss ≥500 mL	62 (12)	56 (11)	36 (9)	20 (23)	-	0.76
No. (%) blood loss ≥1000 mL	9 (2)	10 (2)	6 (2)	4 (5)	-	0.81
No. (%) blood transfusion	9 (2)	11 (2)	6 (2)	5 (6)	-	0.64
Median (IQR) blood loss (mL)	250 (200-350)	250 (200-350)	250 (200-350)	300 (200-425)	250 (200-325)	1.00
No. (%) requiring MROP	11 (2)	15 (3)	12 (3)	2 (2)	1 (11)	0.43
No. (%)requiring further oxytocics	68 (14)	50 (10)	34 (9)	16 (18)	-	0.08
No. (%) with third stage ≥30mins	13 (3)	14 (3)	14 (3)	-	-	0.84
Median (IQR) length of 3rd stage (min)	6 (5-9)	5 (5-9)	5 (4.5-8)	7 (5-10)	5 (5-10)	0.84

* P-value comparing the two randomised arms, i.e. misoprostol and overall "other oxytocic" arms

IQR = inter-quartile range

MROP = Manual removal of placenta

** Relative risk (RR) for blood loss ≥ 500 mL = 0.97, 95% CI = (0.73 - 1.28)

RR for MROP = 0.84, 95% CI = (0.53 - 1.32)

RR for further oxytocic administration = 1.17*, 95% CI = (0.99 - 1.39)

RR for blood transfusion = 0.90, 95% CI = (0.55 - 1.46)

Table 4.5. Mean change in maternal temperature, blood pressure, haemoglobin concentration and haematocrit (after-before delivery) for each of the randomised arms

	Misoprostol n = 501	Other n = 499	p-value
Temperature before delivery	36.5 (0.42)	36.5 (0.40)	
Temperature after delivery	37.1 (0.72)	36.8 (0.49)	
Mean change (SD) in temperature (°C)[1]	0.6 (0.7)	0.3 (0.5)	< 0.001
Systolic BP (mm.Hg) before delivery	118.0 (13.2)	118.9 (13.6)	
Systolic BP (mm.Hg) after delivery	116.7 (13.2)	119.1 (13.1)	
Mean change (SD) in systolic BP (mm.Hg)[2]	-1.3 (12.6)	0.1 (13.0)	0.09
Diastolic BP (mm.Hg) before delivery	74.1 (9.8)	74.2 (9.9)	
Diastolic BP (mm.Hg) after delivery	73.3 (9.0)	73.6 (9.0)	
Mean change (SD) in diastolic BP (mm.Hg)[2]	-0.8 (10.2)	-1.0 (9.9)	0.79
Haemoglobin level (g/dL) before delivery	11.6 (1.1)	11.4 (1.1)	
Haemoglobin level (g/dL) after delivery	10.6 (1.3)	10.4 (1.6)	
Mean change (SD) in haemoglobin level (g/dL)[3]	-1.0 (1.2)	-1.0 (1.6)	0.72
Haematocrit level (%) before delivery	0.349 (0.03)	0.344 (0.03)	
Haematocrit level (%) after delivery	0.319 (0.04)	0.314 (0.05)	
Mean change (SD) in haematocrit level (%)[3]	-0.03 (0.04)	-0.03 (0.05)	1.00

1. n = 432 in the misoprostol arm, and n = 416 in the "other oxytocics" arm.
2. n = 481 in the misoprostol arm, and n = 478 in the "other oxytocics" arm.
3. n = 218 in the misoprostol arm, and n = 236 in the "other oxytocics" arm.

SD = Standard deviation

Table 4.6. Patients' reported side effects for each of the randomised arms

Side effects	Misoprostol n=445	Other n=401	Relative risk (95% CI)	p-value
No. (%) experiencing Shivering	319 (72)	147 (37)	1.95 (1.69, 2.25)	<0.001
No. (%) experiencing Nausea	138 (33)	175 (44)	0.71 (0.59, 0.84)	<0.001
No. (%) experiencing Headache	46 (10)	78 (20)	0.53 (0.38, 0.74)	<0.001
No. (%) experiencing Dizziness	142 (32)	175 (44)	0.73 (0.61, 0.87)	<0.001
No. (%) experiencing Tiredness	335 (75)	341 (85)	0.88 (0.83, 0.94)	<0.001
No. (%) experiencing Vomiting	79 (18)	77 (19)	0.92 (0.69, 1.22)	0.58
No. (%) experiencing Hot flushes	145 (33)	133 (33)	0.98 (0.81, 1.19)	0.83
No. (%) experiencing Abdominal pain	217 (49)	218 (55)	0.89 (0.79, 1.02)	0.10
No. (%) experiencing Diarrhoea	17 (4)	14 (4)	1.09 (0.55, 2.19)	0.80

Table 4.7. Reported shivering by epidural analgesia among the randomised arms

	Misoprostol	Other	RR (95% CI)
In subgroup receiving epidural analgesia No. (%) reporting shivering	n = 197 154 (78%)	n = 187 76 (41%)	1.91 (1.59, 2.31)
In subgroup not receiving epidural analgesia No. (%) reporting shivering	n = 248 165 (67%)	n = 214 71 (33%)	2.00 (1.62, 2.46)

Table 4.8. Median severity* (IQR) of each reported side effect by randomised arm

Side effects	Misoprostol	Other	p-value**
Shivering	4 (2-4)	2 (1-3)	< 0.001
Tiredness	2 (2-4)	3 (2-4)	0.10
Dizziness	2 (1-3)	2 (1-3)	0.71
Headache	1 (1-2)	1 (1-2)	0.08
Nausea	2 (1-3)	2 (1-3)	0.14
Vomiting	3 (2-4)	3 (2-4)	0.47
Hot flushes	2 (1-3)	2 (1-3)	0.27
Abdominal pain	2 (1-3)	2 (1-3)	0.65
Diarrhoea	2 (1-3)	1 (1-3)	0.73

* Severity was scored on a scale from 0 (none) to 4 (very severe)

** By the Mann-Whitney test

IQR = Inter-quartile range

Appendix 4.A: Data collection form; including patient information sheet, consent form, and information to doctors and midwives

The third stage trial

Department of Obstetrics and Gynaecology

UCL

1996

Contents:

Information for doctors and midwives

Patient information sheet

Consent form → To be kept in patient's notes.

Data collection form → To be kept in data box in labour ward computer room

Self-filling questionnaire

Information for Doctors and Midwifery Staff

The Third stage study

Background Information

- Misoprostol is a widely used drug with a well known safety record in the field of peptic ulcer disease.
- Its trade name is Cytotec. More information is available about the drug in the BNF in the section entitled 'Ulcer healing agents' (page 20-30 depending on the edition). It is also present in another form called Arthrotec. This is a combination of Diclofenac and Misoprostol.
- Prostaglandins administered parenterally are known to be effective in treating intractable post partum haemorrhage. Misoprostol is a Prostaglandin E1 analogue in tablet form.
- The absorption of misoprostol is very quick. It reaches its peak level in the circulation within minutes. *See graph in labour ward.*
- This is a randomised trial examining the efficacy of misoprostol versus other treatments in the management of the third stage. We have previously examined the efficacy of misoprostol for this purpose in more than 400 patients. The results are encouraging. The incidence of PPH was similar to that when syntometrine is used.

YOU NEED TO

What you need to do is

- Speak to patient
- Consent
- Open the envelope when it is clear that delivery will be vaginal

- All women delivering in this hospital are potentially eligible. The only exclusion criteria are women in whom caesarean section are planned.
- If the envelope reads **M** : Your patient will be in the misoprostol arm. (500 ug. orally)
- If the envelope reads **O** : this patient will receive syntometrine unless she is:
  Hypertensive where she will receive ⇒ Syntocinon 10 IU IM
  Para 4 or more where she will receive ⇒ Ergometrine 500 μg IV
- In Twin cases the treatment will be given as usual after the delivery of the second twin.
- If the patient was receiving syntocinon drip during labour, You need to stop it .
- Patients will have IV cannula as per hospital protocol if she is Para 5 or more or if she has history of PPH (whether she is having misoprostol or Ergometrine)

When should you administer the drug and How

Misoprostol: Deliver the Baby, clamp and divide the cord and immediately give patient 500 μgm Misoprostol (two and a half tablets) by mouth. Placenta is to be delivered by controlled cord traction as usual.

Other drugs: O arm will receive the drugs as usual

Documentation

- The above dose should be documented in the patients drug chart.
- Midwife in charge of the case needs to fill data collection form document.
- Ensure that data collection forms and Patient's Questionnaire are kept aside for collection.

* Women with high parity or cardiac disease will still enter the randomisation & will receive either misoprostol or syntocinon depending on the randomisation.

* Women with hypertension will also be elegible to randomisation. They will receive either misoprostol or syntocinon.

Patient Information Sheet

The Third Stage Trial

At the Obstetric (maternity) hospital we are always looking for ways of improving the care we give to mothers and their babies.

One area which we are looking into at the moment is the way in which the afterbirth (placenta) is delivered. The time during birth when this happens is called the third stage of labour. At this stage of labour women are more likely to bleed than at any other time of their labour and hence they are usually given an injection as the baby is born.

Unfortunately there are a number of problems associated with this treatment: This treatment is given as an injection which you might not like; the injection is known to increase the blood pressure and on occasions it can cause a feeling of sickness. In this country disposable clean needles are used all the time, in other parts of the world this may not be possible. If that happens the injection can transmit disease.

Recently it has been discovered that tablets (made from a substance called prostaglandin) can bring about quick contraction of the womb. These tablets are given by mouth. During 1995 we have conducted a study examining how effective these tablets are at reducing the blood loss after delivery. We now know that the tablet method is practical, effective and safe. The main undesired symptom is that you might feel cold and shivery after delivery. We feel very encouraged by the results but we need to compare the two treatments directly to know which is better.

If you agree to join the study this is what will happen: On admission to the labour ward a small blood sample will be taken from you. After the delivery of your baby and clamping the cord you will either receive an injection Or you will receive three tablets to swallow. We know that both treatments work but we would like to know which one is better. We will not know which treatment you will receive until you are actually approaching delivery. After your delivery and before discharge home another blood sample will be taken from you, the purpose of which is to compare it with the sample taken from you the day before. There is no follow up required but we will be happy to review you and answer all queries any time you like.

You do not have to take part in the study if you do not want to. If you decide to take part you may withdraw at any time without having to give a reason. Your decision whether to take part or not will not affect your care and management in any way.

Thank you for your help

Consent Form

Third stage study

Have you read the information sheet about this study Yes/No

Have you had the opportunity to ask questions and discuss study Yes/No

Have you received satisfactory answers to all your questions? Yes/No

Have you received enough information about this study? Yes/No

Which doctor have you spoken to about this study? Dr----------

Do you understand that you are free to withdraw from this study

i) at any time Yes/No

ii) without giving a reason for withdrawing Yes/No

Do you agree to take part in this study?

Signed.....Date.....

Name in block letters.....

Doctor/Midwife.....
Signed.....

To be filled by midwife

Affix a sticker or write

patient name | Date | Midwife name

unit number | Age | Parity | Gestation

unit number | height | Last recorded weight

Did your patient have history of PPH or retained placenta in previous pregnancies? Yes/ No

---

Did your patient receive **M**isoprostol or **O**ther treatment

1 Misoprostol
2 Syntometrine
3 Syntocinon
4 Ergometrine

In my opinion the estimated blood loss during delivery and during the first hour after delivery was .....mls.

I

Features of labour

Please write the length of first and second stages: First.....Second.....

Did your patient have the following:

Prostin pessaries	Yes/No
Syntocinon augmentation	Yes/No
Epidural anaesthesia	Yes/No
Narcotic analgesia	Yes/No
Anti emetic injections	Yes/No

Did your patient feel sick during labour Yes/ No

Did your patient vomit during labour Yes/ No

If your patient Vomited during labour Once/ twice/ more

Did Your patient vomit after or before having Epidural anaesthesia Before/ After

---

Did Your patient feel cold or shiver during labour (prior to the third stage) Yes/No

If yes Did Your patient feel cold or shiver before (or without) or after epidural anaesthesia. Before/ After

---

II

Features of delivery

SVD without Episiotomy Baby's weight
SVD + Episiotomy
Ventouse without episiotomy
Ventouse + Episiotomy
Forceps
Kielland forceps

Tears First degree Second Third

III

Features of placental delivery

Information regarding Cord traction

Circle one or more

1 No cord traction
2 within 30 seconds after delivery
3 Before signs of separation
4 After signs of separation

Who managed the third stage ?

1. Consultant
2. Other medical officers
3. Registered midwife
4. Student midwife
5. Medical student

a The placenta was delivered

1 Normally
2 Retained placenta (if retained placenta please answer the following)

i Placenta delivered in theatre after (...) minutes of the delivery of the baby

ii Did the patient receive further oxytocics (misoprostol / Syntometrine / Ergometrine / None)

iii If so did she receive them because (She was bleeding / To help expel the placenta / Other *Please specify:*_____)

b. Placenta Length of third stage .....

Manual removal of placenta Yes / No

IV

Blood pressure

Is this patient a known hypertensive? *Yes / No / Unsure*

Has this patient suffered from Preeclampsia or pregnancy induced hypertension during this pregnancy *Yes / No / Unsure*

Last measured BP prior to delivery

BP one hour after delivery

V

Temperature

Last measured temperature prior to delivery

Temperature one hour after delivery

Temperature prior to discharge to the ward

VI

Vomiting

Did your patient vomit during labour (i.e. prior to the delivery of the placenta)?

Did your patient vomit within one hour of receiving the trial treatment?

VII

Did your patient require any analgesia for 'after pains' Yes or No

Specify type of analgesia .....

To which postnatal ward was the patient admitted ?

Did the patient fill the Questionnaires?

Appendix 4.B: Patients' Questionnaire

To be filled in by the patient one hour after delivery

Patient Details (*Affix a sticker or write*)

Please write your name Date Time

To what extent, if at all, you have experienced the following symptoms since you have delivered today? For each symptom please circle the number which best describes the extent to which you have experienced that symptom. Even if none of the numbers seem exactly right to you choose the one that is closest to your experience. Please be sure to circle the one number for each symptom. Remember we are only interested in your experience as you see it , so there are no 'right' or 'wrong' answers.

I have experienced this		0 = not at all 1 = mildly 2 = moderately 3 = quite strongly 4 = very strongly				
1	Nausea	0	1	2	3	4
2	Headache	0	1	2	3	4
3	Hot flushes	0	1	2	3	4
4	Dizziness	0	1	2	3	4
5	Vomiting	0	1	2	3	4
6	Tiredness	0	1	2	3	4
7	Diarrhoea	0	1	2	3	4
8	Abdominal pain	0	1	2	3	4
9	Shivering	0	1	2	3	4

Please attach to the front of patients notes if completed
or put in collection box, please ensure that patient name is completed

Chapter 5

Pyrexia and shivering among parturient women following administration of oral Misoprostol versus Other oxytocics for management of the third stage of labour.

Background

Shivering and pyrexia were identified as the two main side effects to oral misoprostol administration in the third stage of labour. These two side effects were obvious in the intrauterine pressure study (chapter 2), the pilot studies (chapter 3), and the randomised controlled trial (chapter 4). In the pilot studies, shivering occurred in 62% of patients receiving the 500 and 600 μgm doses, and 41% of those receiving the 400 μgm dosage. In the randomised trial, shivering was seen among 72% of women receiving oral misoprostol, which was twice as much as among those receiving other oxytocics (37%). In the field of abortion, the use of much higher misoprostol dosages was not associated with shivering.

Shivering is a recognised symptom that is known to occur during or immediately after normal delivery. Jaameri (1966) reported a shivering rate of 22.7% among women with normal deliveries. It was reported to occur in the immediate postpartum period, and its incidence was significantly higher among multiparous women of older ages. Low maternal body weight and inadequate amounts of amniotic fluid appeared to predispose to shivering (Jaameri, 1966).

Shivering occurs as a temperature raising mechanism so as to increase heat production in response to hypothermia. The primary motor center for shivering is located in the posterior hypothalamus. This area is inhibited by signals from the heat center in the Anterior Hypothalamic-Preoptic region (AH/PO), and is stimulated by cold signals from the skin and spinal cord. This area becomes activated when there is a fall in body temperature, after which signals are transmitted through bilateral tracts down the brain stem into the lateral columns of the spinal cord, and finally into the anterior motor neurons,

thereby causing shivering. These signals are non-rhythmical and do not cause the actual muscle to shiver, but increase skeletal muscle tone throughout the body by facilitating the activity of the anterior motor neurons. Shivering begins when skeletal muscle tone rises above a certain critical level. During the peak of shivering, body heat production can rise up to four or five times normal levels (Guyton & Hall, 1996).

The incidence of shivering is known to increase in association with regional anaesthesia, during which it rises up to 33 - 60% (Morgan *et al.*, 1984; Brownridge, 1986; Buggy & Gardiner, 1995). The mechanism by which shivering occurs in association with epidural analgesia is thought to be thermogenic (Scherer, 1997).

Anaesthesia and surgery are known to impair the process of thermoregulation. All volatile and intravenous anaesthetics, opioids, in addition to spinal and epidural analgesia induce hypothermia. Following induction of general, spinal, or epidural anaesthesia, core temperature significantly decreases as a result of internal redistribution of body heat from the core thermal compartment to peripheral tissues, and a net loss of heat to the environment. Lowered core body temperatures between 33 to 35°C leads to peripheral thermoregulatory vasoconstriction to slow the loss of heat. This is followed by shivering, which raises body temperature by increasing muscle tone and oxygen uptake.

In case of general and spinal anaesthesia, it is thought that a real reduction in body heat occurs about one hour after induction of anaesthesia and initial redistribution hypothermia due to heat loss exceeding metabolic heat production. Heat loss further increases due to low operating room temperatures, evaporation from open body cavities, and cold IV fluids. Body heat content continues to decrease even though core temperatures remain

almost constant after their initial drop. However, in case of epidural anaesthesia, redistribution remains the major cause of hypothermia. Even after 3 hours of induction of anaesthesia, core temperature decreases only half as much as during general anaesthesia, because the metabolic rate is maintained and the arm vessels remain vasoconstricted (Matsukawa *et al.*, 1995). Chan *et al.* (1989) reported that the peak onset of shivering occurs within 10 minutes of epidural anaesthesia, and precedes any significant decline in core temperature.

A contrasting opinion suggests that, unlike epidural anaesthesia for caesarean section or general surgery, epidural anaesthesia in labour leads to maternal hyperthermia rather than hypothermia. Multiple influencing factors are thought to be involved, such as the site at which temperature is measured, ambient temperature, duration of previous labour, cervical dilatation at the time of epidural puncture, and the occurrence of shivering. This view proposes that, during the first two to five hours of epidural analgesia, there is a weak, if any, increase in temperature. If labour is prolonged, especially in case of primiparae, a linear increase in temperature occurs with time, at a mean rate of 1°C every seven hours. However, the pathophysiology of this rise in temperature is still hypothetical. It is thought, however, that heat loss through sweating and hyperventilation in labour is reduced by epidural analgesia, and is therefore surpassed by labour-induced heat production. This hyperthermia has been correlated with fetal tachycardia, but not with any infectious process (Mercier & Benhamou, 1994).

Fever occurs when the thermoregulatory set-point of the hypothalamus is shifted upward due to the effect of pyrogenic substances released from toxic bacteria, tissue destruction, dehydration, or under the influence of drugs. When this set-point increases to a higher level than normal, all the

mechanisms responsible for raising body temperature are activated. This includes increased heat production and conservation. Within a few hours, body temperature increases to reach the higher set-point level. During this time, a person experiences chills and feels extremely cold, even though body temperature may have already risen above normal. As a result of vasoconstriction, the skin becomes cold, piloerection occurs, epinephrine is secreted, and the person starts to shiver. Chills continue until body temperature reaches the new hypothalamic setting. As long as the factor causing the rise in the hypothalamic set-point remains, body temperature is regulated as normal, but at the higher set-point level. However, if the factor causing the increase in temperature is suddenly removed, the set-point of the hypothalamic temperature-regulating center is reduced to a lower level or back to normal. In this case, body temperature is still elevated, but the hypothalamus attempts to regulate it back to normal. This leads to intense sweating, and as a result of generalised vasodilatation, the skin becomes hot or "flushing" occurs, after which the temperature starts to fall (Guyton & Hall, 1996). It is believed that endogenous pyrogens trigger the elevation of the hypothalamic set-point, the mechanism of which remains unclear. However, prostaglandins have been implicated in playing a role in this mechanism.

Pyrexia is a well-recognised centrally mediated prostaglandin side effect (Milton & Wendlandt, 1971; Veale & Cooper, 1975; Jain & Mishell, 1994; Haberal *et al.*, 1996; Creinin *et al.*, 1997 a, b; Srisomboon *et al.*, 1997 a). Prostaglandins of the E-series (PGE_2), in particular, are essential mediators in the central action of pyrogens and the initiation of fever. Prostaglandins are naturally present in the hypothalamus and in the cerebrospinal fluid. Milton & Wendlandt (1971) were the first to propose that pyrogens may induce fever via the production of specific prostaglandins, and that drugs which reduce fever (antipyretics) do so by blocking the synthesis and release of prostaglandins.

They reported that direct injection of minute amounts of prostaglandins E_1 and E_2 into the cerebral ventricular system of cats and rabbits, produced a sharp rise in body temperature, and extreme hyperthermia in a few minutes, even with quantities as low as 100 pg. Other related prostaglandins e.g. $F_{2\alpha}$, A_1, on the other hand, failed to produce fever. Hales *et al.* (1973) and Feldberg and Saxena (1975) confirmed that intraventricular injections of PGE_1, PGE_2, $PGF_{1\alpha}$, and $PGF_{2\alpha}$ induced fever in sheep and rats.

It is thought that prostaglandins of the E series are synthesised and released in the tissues of the anterior hypothalamic/preoptic (AH/PO) region, and are involved in the fever produced by injection of intravenous pyrogen. The AH/PO region of the brain is thermally sensitive, responsive to pyrogens, and is thought to be responsible for the integration of thermal information. It is the most sensitive area of the brain to the hyperthermic effect of direct application of PGE_1, PGE_2, and endogenous pyrogen. However, it has been suggested that the AH/PO region is not the sole centre for temperature regulation. Some investigators have reported that surgical ablation or lesioning of the AH/PO region had little effect on the febrile response. Veale & Cooper (1975) reported that following removal of the entire AH/PO in rabbits, an IV injection of an endogenous pyrogen still produced a fever, that was of similar magnitude to that occurring in control rabbits. However, injection of prostaglandins in the area of the lesioned AH/PO no longer produced a rise in body temperature.

Gollman and Rudy (1988) investigated the incidence of pyrexia in response to direct injection of various prostanoids and prostanoid-mimetics into the AH/PO region of conscious cats pretreated with indomethacin, which is known to suppress the production of PGE_2 in the brain. Three E-series prostaglandins; PGE_2, PGE_1, and 6-keto-PGE_1, were reported as potent

mediators of pyrexia. Very low doses of these prostaglandins, between 2 and 15 pmol, were required to produce a 1°C rise in temperature. Since PGE_2 is abundantly produced in the cat brain, it is understood that predominantly PGE_2 and, to a lesser extent, PGE_1 play an important role in the production of fever.

It has been clinically proven that antipyretics such as aspirin, acetaminophen, or ibuprofen are effective in reducing fever as a result of inhibition of the synthesis of prostaglandins (Murphy, 1992). The mechanism by which prostaglandins increase heat production, and their effect on heat conservation pathways, however, are still uncertain.

Fever has not been reported in association with oral misoprostol use in the treatment of duodenal ulcer or rheumatoid arthritis. The only reported side effects to the use of 400 to 800 ugm/day of oral misoprostol in divided doses are mainly gastrointestinal, such as abdominal cramps and mild self-limiting diarrhoea (Dajani *et al.*, 1991; Lanza *et al.*,1991; Geis, 1992; Numo, 1992; Gagnier, 1993; Melo Gomes *et al.*, 1993). The only report on the pyrogenic effect of oral misoprostol is that by Baulieu *et al.*, (1992) where recurrent bouts of pyrexia occurred after misoprostol administration in a cirrhotic patient.

However, fever has been reported as a side effect to misoprostol in the field of abortion and mid-trimester termination of pregnancy. Haberal *et al.* (1996) reported fever as a side effect to oral misoprostol while investigating doses ranging from 200 up to 1200 μgm in induction of early abortion. Other reported side effects were nausea, vomiting, diarrhoea, hypotension, headache and abdominal pain. El-Refaey *et al.* (1995 a) reported a 45% incidence of pyrexia with the use of 800 μgm of vaginal misoprostol and subsequent 400 μgm oral doses at three hourly intervals to a maximum of four doses in

induction of abortion. Nausea was seen in 50%, vomiting in 40%, and diarrhoea in 20% of patients.

Creinin *et al.* (1997 b) conducted a prospective multicenter trial on 300 women, investigating the safety and efficacy of 50 mg of oral methotrexate followed 5-6 days later by 800 μgm of vaginal misoprostol, for medical abortion. Reported side effects after misoprostol administration were nausea in 33%, vomiting in 18%, diarrhea in 18% and subjective fever or chills in 31% of patients.

In second trimester abortion studies, Jain and Mishell (1994) compared the safety and efficacy of 200 μgm of intravaginal misoprostol, administered every 12 hours, with that of 20 mg of intravaginal PGE_2 dinoprostone, administered every 3 hours, in a prospective randomised trial on 55 women between 12 to 22 weeks of pregnancy. Side effects occurred more frequently among women receiving PGE_2 than those receiving misoprostol, including pyrexia (63% compared to 11%; p-value < 0.001), uterine pain (67% compared to 57%, p-value = 0.58), vomiting (33% compared to 4%, p-value = 0.005), and diarrhoea (30% compared to 4%, p-value = 0.012). Srisomboon *et al.* (1997 b) investigated the use of 200 μgm of misoprostol gel administered intracervicovaginally every 12 hours to achieve mid-trimester pregnancy termination on 50 women between 14 to 27 weeks gestation. Reported side effects were fever (8%), nausea and vomiting (6%) and diarrhoea (2%).

Hyperpyrexia, on the other hand, may lead to grave, life-threatening consequences. Hyperpyrexia and hyperthermia are synonyms, and are defined as a rise in body temperature to 41.1°C and above, with accompanying central nervous system signs and absence of sweating (Price, 1979; Rodgers, 1983; Samiy *et al.*, 1987). Fever, in contrast to hyperthermia, results from an upward

adjustment of the hypothalamic set-point in response to pyrogens or other factors. Fever usually responds to antipyretic agents, and has diurnal variation. In comparison, hyperthermia patients have a persistent elevation of temperature without much fluctuation, and with no significant response to antipyretic agents (Samiy *et al.*, 1987).

Causes of hyperpyrexia include exposure to heat, dermatologic impairment of heat loss, spinal cord injuries, burns, chronic diseases of the heart, lungs, and kidneys, and diabetes. Nutritional deficiencies, acute and chronic motor disorders, use of psychotropic agents, diverse toxicologic agents, inhalation anaesthesia, pyrogenic stimuli, and drug interactions may all cause hyperpyrexia (Greenblatt, 1978; Samiy *et al.*, 1987). Malignant hyperpyrexia is a condition that develops as a complication to general or inhalation anaesthesia, and is rapidly fatal. Its main manifestations are a rapid rise in body temperature, widespread muscular rigidity, and severe metabolic acidosis. It occurs mainly in the operating room or in the postoperative period. In this case, severe muscle contraction results in myonecrosis with an accompanying increase in serum myoglobin and myoglobinuria, which is complicated by acute renal failure (Gronert, 1980; Rodgers, 1983).

The onset of clinical symptoms of hyperpyrexia is abrupt and usually without prodromal symptoms. In its mild form the patient is conscious and sweating, and may complain of intense thirst, headache, dizziness, and restlessness. The full picture is characterised by cerebral signs and symptoms, hot dry skin, and very high oral and rectal temperatures. The patient becomes increasingly restless, disoriented, delirious, or comatose. Convulsions or muscular twitching of the limbs may occur. The signs of cerebral involvement vary in form and intensity in individual patients, and their severity usually depends on the degree and severity of the high fever. The skin is usually flushed,

occasionally pale, and dry over the whole body due to absence of sweating. Cyanosis of the lips and face is common. The oral temperature is 41.1°C or above, and the rectal temperature is about 0.6°C higher. The pulse becomes rapid; 130 beats or more per minute, with a high respiratory rate. The blood pressure remains normal unless shock has ensued. In hyperpyrexia cases, severe muscle contraction results in rhabdomyolysis with an accompanying increase in serum myoglobin and myoglobinuria. Furthermore, as a result of destruction of red blood cells and intravascular haemolysis, haemoglobin is released into the blood stream. Circulating free haemoglobin and myoglobin in the plasma is commonly complicated by acute renal failure. In late stages accompanying shock, there may be anuria, uraemia, and progressive evidence of pulmonary oedema (Samiy *et al.*, 1987).

Treatment of hyperpyrexia is accomplished by effective cooling to reduce the rectal temperature to about 38.9°C, within one hour of the onset of symptoms. The patient is covered by a light sheet and sprayed with cool water while moving air from an electric fan or natural sources encourages evaporation, or alternatively, the naked patient is placed in a tub containing water and ice chips. The body and limbs should be massaged during cooling to promote the peripheral circulation. Consciousness usually returns by the end of cooling, with improvement in breathing and pulse rate. If shock ensues, measures should be taken to treat the shock. Untreated cases of hyperpyrexia usually die, as a result of the high temperature or from shock, within two days in the majority of cases. If cases are adequately treated in time the mortality is low, the prognosis depending on the height and duration of fever before start of treatment, and on the development of shock (Samiy *et al.*, 1987).

All the studies reporting cases of misoprostol toxicity or overdosage indicated hyperpyrexia and tremors as major symptoms, hyperpyrexia being contributed

to the direct effect of the drug. Graber and Meier (1991) reported fever (temperature of 39.2°C) as a major symptom of misoprostol toxicity, along with shivering and tremors, hyperreflexia, tachycardia, hypertension, nausea, and abdominal cramps. Bond and Van-Zee (1994) reported hyperpyrexia (temperature of 41.3°C) along with uterine contraction and fetal death, tachycardia, rhabdomyolysis, hypoxemia, respiratory alkalosis, and metabolic acidosis after overdosage with 30 tablets of 200 μgm of misoprostol and 4 tablets of 2 mg trifluoperazine (Stelazine) in a suicide attempt. Austin *et al.* (1997) reported a rise in temperature up to 41.4°C within 3.5 hours of administration of 6000 μgm of misoprostol intravaginally, and 600 μgm orally. Associated symptoms included shivering and chills, abdominal and extremity cramping, hypotension, vomiting, and confusion.

In the randomised controlled trial (chapter 4), the shivering rate was twice as high in the misoprostol arm as in the "other oxytocics" arm (72% compared to 37%, RR = 1.95, 95% CI of 1.69 to 2.25, p-value < 0.001). Among women receiving oral misoprostol, the incidence of shivering was significantly higher in those who had received epidural analgesia compared to those who had not (78% compared to 67%, p-value = 0.01). Pyrexia was the second most prominent side effect associated with oral misoprostol use in the third stage of labour. In the pilot studies (chapter 3), the rise in temperature was seen with all the dosages investigated, and ranged from 0.5°C to 0.7°C. In the randomised trial, a statistically significant increase in mean temperature of about 0.6°C was seen in the misoprostol arm, in comparison to an increase of only 0.3°C in the "other oxytocics" arm. 4.9% of women in the misoprostol arm experienced a statistically significant rise in temperature of ≥ 2°C, compared with only 0.2% in women receiving "other oxytocics" (p-value < 0.001). However, it was not known whether the rise in temperature occurred secondary to the shivering, or as a direct action of the prostaglandin itself.

While the randomised controlled trial was in progress, the high incidence of shivering and rise in temperature among women in the oral misoprostol arm prompted us to investigate further into their occurrence. It was essential to find out how soon after drug administration shivering and pyrexia occurred, the duration of shivering, in addition to any likely influencing factors such as epidural analgesia in labour. It was important to study the relationship between shivering and pyrexia; whether shivering contributed to the occurrence of pyrexia as a secondary response, or if the pyrexia occurred independently as a direct influence of the prostaglandin. It was important to address both these issues so that plans for intervention could be devised if needed.

Patients and methods

Patients in this study were recruited from women who had given consent to participate in the third stage randomised controlled trial conducted at The Obstetric Hospital, U.C.H. The main objective of this study was to investigate and compare the incidence of shivering and pyrexia among women receiving misoprostol or "other oxytocics" for management of the third stage of labour. We also wanted to understand the relationship between this sign and symptom, hoping to find out which one occurred first, and the onset and duration of each.

After consenting to the randomised trial, this study was discussed with the patients, and women were recruited if they agreed to participate. When delivery was imminent, a randomisation envelope was picked from a previously prepared batch. Envelopes marked with "M" were randomised to receive 500 μgm of oral misoprostol tablets, and those marked with "O" were randomised to receive another oxytocic agent; syntometrine, syntocinon, or

ergometrine, depending on maternal condition, immediately after delivery of the baby and clamping and dividing of the cord.

Each patient's temperature and pulse were measured by the principle investigator, who also completed the data collection sheet (Appendix 5.A). The time of onset of shivering, which was a clear and explicit event, was recorded, along with its decline, which was assessed both by the investigator and by each patient's subjective account. After delivery and administration of the allocated oxytocic, each woman's temperature and pulse were measured at 15-minute intervals for one hour, then at two hours and three hours after delivery.

Shivering was assessed clinically, in accordance with most studies in the literature that have evaluated shivering rates by subjective assessment. It was defined as a visible tremor of the head, neck, trunk, or limbs. The occurrence of shivering and its duration, and the time interval from delivery to start of visible shivering were documented for both study groups. Pyrexia was defined as a rise in temperature over 37.5°C, at any time after delivery within the observation period. Its detection and the time interval from delivery to rise in temperature were documented for both study groups.

The data collection sheet also contained information on maternal characteristics such as age, parity, and gestation at delivery. Labour variables included whether it was spontaneous or induced, whether rupture of membranes was spontaneous or artificial and time it occurred, and whether labour was augmented by syntocinon. Information on whether the mother received epidural analgesia in labour, whether the mother felt cold in labour, before or after epidural, or after delivery. The lengths of the first, second, and third stages of labour were also documented. Third stage variables included

information on administration of antiemetics or analgesics for after-pains, and the frequency of side effects such as nausea, vomiting, pyrexia, and shivering in each arm.

Statistical methods

Continuous variables that are normally distributed are presented as means and standard deviations (SD). Continuous variables that are not normally distributed are presented as medians and inter-quartile ranges (25^{th} - 75^{th} percentile). Continuous variables were compared with student's t-test, and the changes in temperature and pulse before and after administration of the trial drug were assessed by the paired sample t-test. Data for categorical variables are presented as numbers and percentages. Associations were assessed using the chi-squared test or Fishers exact test, as appropriate.

Results

The total population included in the study was 62 patients; 32 received 500 μgm of Misoprostol orally, and 30 received "other oxytocics". In this group, 24 women received syntometrine, and 6 received syntocinon. Table 5.1 demonstrates baseline characteristics and obstetrical history of patients in the two study groups. Both groups were comparable in terms of maternal age, parity, and gestation at delivery.

Table 5.2 represents a comparison of events in labour between the studied groups. The two groups appeared comparable in terms of labour events, and there were no statistically significant differences between the two groups.

Although the difference in the time interval between rupture of the membranes and delivery, and that between induction of epidural analgesia and delivery in the misoprostol group appeared longer than the other oxytocics group, the differences were not statistically significant. The length of labour was also comparable between the two groups.

Table 5.3 represents a comparison of third stage variables and frequency of side effects between the two studied groups. Nausea occurred more frequently among women in the "other oxytocics" group (40% compared to 31%, p-value = 0.60) but was not statistically significant. Vomiting was twice as high in the "other oxytocics" group but also was not statistically significant (7% compared to 3%, p-value = 0.61). Four women (13%) in the "other oxytocics" group received antiemetics in the third stage compared to none in the misoprostol group (p-value < 0.05). A higher number of women in the misoprostol group received analgesics for after-pains, but was not statistically significant (47% compared to 30%, p-value = 0.20).

Table 5.4 represents a comparison of cold and shivering sensation in labour and after delivery between the two study arms. The number of women experiencing a sensation of cold and shivering in labour was almost similar in the two arms (22% compared to 20%, p-value = 0.86). Cold sensation after delivery was reported more often among women receiving misoprostol but was not statistically significant (41% compared to 33%, p-value = 0.56).

The most prominent side effect of misoprostol was shivering (Table 5.4), which occurred significantly higher than among the "other oxytocics" group, 78% compared to 13%, p-value < 0.001 (RR of 5.86, 95% CI of 2.3 to 14.9). The occurrence of shivering among women receiving oral misoprostol was not associated with feeling cold in labour or after delivery (p - value = 0.20).

However, cold sensation after delivery was reported by all the shiverers in the "other oxytocics" group (p-value < 0.001) (Table 5.5).

Among women receiving oral misoprostol, shivering occurred within 5 to 58 minutes of delivery. It started within a mean time of 18 min. (SD = 13, Median = 15 min., IQR = 10 - 24), and its mean duration was 33 min. (SD = 22.0, median = 30 min., IQR = 20 - 35). The longest duration of shivering in the misoprostol group was 115 min. in one patient (Table 5.4). In the "other oxytocics" group, shivering occurred in 4 cases, and the mean delivery to shivering interval was 14 minutes (SD = 10, Median = 20 min.) The duration of shivering was significantly higher among women in the misoprostol group (33 min. compared to 8 min., p-value = 0.02). The difference in mean delivery to shivering interval between the two studied groups was not statistically significant (p-value = 0.60).

The most commonly used type of epidural analgesia was the Low Dose Mixture (LDM) of 0.1% Bupivacaine HCL (Mercaine) and Fentanyl 2μgm/mL. The higher incidence of shivering among the misoprostol group remained even after control for epidural analgesia in labour (p-value < 0.001) (Table 5.6). In the misoprostol group, all the 17 women (100%) who had received epidural analgesia shivered. Among the other 15 who did not have epidural, 8 (53%) women shivered. In the "other oxytocics" group the shivering rate was the same regardless of whether women received epidural analgesia in labour or not.

The second most prominent side effect was pyrexia (temp. > 37.5°C), which was significantly higher in the misoprostol group, occurring in almost half the patients (47%), compared to four women in the "other oxytocics" group (13%), p-value < 0.001 (RR of 3.5, 95% CI of 1.3 to 9.4). The highest

temperature in the misoprostol group was 39.8°C, which was measured at 45 min. after drug administration in one patient. Tables 5.7, 5.8, 5.9, and 5.10 demonstrate the frequency of pyrexia, and the changes in temperature between the two study groups. In the misoprostol group the mean time interval from delivery to the rise in temperature was 33 minutes (SD = 11, Median = 30 min., IQR = 30 - 45) (Table 5.7). In the "other oxytocics" group, pyrexia occurred in 4 cases, and the mean delivery to pyrexia interval was 45 minutes (SD = 12, Median = 45 min., IQR = 34 - 56) (Table 5.7). The difference in mean delivery to pyrexia interval between the two groups showed borderline significance (p-value = 0.05).

In the misoprostol group (Table 5.8), a significant rise in temperature is noticed within the first 15 minutes of drug administration, and again in the 30 to 45 minute interval. When mean temperature before delivery (36.4°C) was compared to that measured at 15 min. (37.1°C), a significant rise in temperature of about 0.7°C (p-value < 0.001) was noted. When mean temperature at 30 min. (37.1°C) was compared to that at 45 min. (37.8°C), there was a significant rise in temperature of about 0.6°C (p-value = 0.04). After 2 hours of delivery, the mean temperature (37.6°C) remained significantly higher than that measured before delivery by about 1.2°C (p-value < 0.001). In the "other oxytocics" group, there were no significant differences in temperature measurements within the observation period.

Table 5.10 demonstrates the differences in mean rise in temperature between the two study arms at different intervals after delivery. The highest difference in mean temperature was seen at 45 min. and at 60 min. of delivery, amounting to a difference of 1.0°C (95% CI of 0.66 to 1.41, and 0.64 to 1.41 respectively).

Pyrexia was significantly associated with receiving epidural anaesthesia in labour (Table 5.11). In the misoprostol group, 11 of the 17 women (64.7%) who had epidural anaesthesia developed pyrexia, compared to only 4 (26.7%) of the 15 with epidurals in the "other oxytocics" group (p-value < 0.05).

Shivering was significantly associated with pyrexia among women receiving oral misoprostol (Table 5.12). Among the 25 women (78%) who shivered in the misoprostol group, 15 (60%) developed pyrexia, and 10 (40%) did not. None of the non-shiverers (7 women, 22%) developed pyrexia (p-value < 0.001). In the "other oxytocics" group, none of the 4 women (13%) who shivered developed pyrexia (p-value = 1.0). A clear association was found between shivering and the rise in temperature in the misoprostol arm. F-test of interaction between shivering and randomised group on the change in temperature = 7.2, p-value < 0.001. The difference in mean change in temperature between shiverers and non-shiverers in the misoprostol group is demonsrated in Table 5.13. Shivering and pyrexia occurred more often among women receiving epidural analgesia in the misoprostol group (11/17 or 65%) (Table 5.14).

Table 5.15 demonstrates the incidence of pyrexia and shivering among women receiving postpartum analgesia in the two compared groups. There was a higher percentage of women receiving postpartum analgesia in the misoprostol group, 47% compared to 30% among women receiving other oxytocics, but this difference was not statistically significant (p-value = 0.20) (Table 5.3). There was a significantly higher incidence of shivering among women receiving analgesics in the misoprostol group; 80.0% compared to 11.0% among women receiving other oxytocics (p-value = 0.002). The incidence of pyrexia was also higher among women receiving analgesics in the misoprostol

group; 40.0% compared to 11.0% among women receiving other oxytocics, but this difference was not statistically significant (p-value = 0.20).

Discussion

This study aimed to investigate the occurrence of shivering and pyrexia as side effects to orally administered misoprostol in the third stage of labour, their temporal relationship, if present, and the effect of other influencing factors such as epidural anaesthesia in labour.

In the randomised controlled trial (chapter 4), the shivering rate among women receiving oral misoprostol was significantly higher than that among women receiving "other oxytocics" (72% compared to 37.0%, p-value < 0.001). This high shivering rate in the misoprostol arm was associated with a significantly high incidence of pyrexia, such that 28% of those who shivered developed pyrexia, compared to 10% among non-shiverers (p-value < 0.001).

This study confirmed that oral misoprostol administered in the third stage of labour was associated with a significantly high incidence of shivering (78%; RR of 5.86, 95% CI of 2.3 to 14.9) and pyrexia (47%; RR of 3.5, 95% CI of 1.3 to 9.4). Shivering occurred within 5 to 10 minutes of delivery (Median = 15 min., IQR 10 - 24 min.), and lasted for about 20 to 40 minutes (median duration was 30 min., IQR 20 - 35 min.). The longest duration of shivering was 115 min. in one woman. However, it was self-limiting, and did not require any medical intervention. A significant rise in temperature was obvious within the first 15 minutes of delivery, followed by a second significant rise occurring shortly after the onset of visible shivering. The mean time interval from delivery to the second episode of pyrexia was 33 minutes (SD = 11).

Pyrexia was therefore seen to occur both before and after the shivering episode. It could be that misoprostol produces a rise in temperature, in addition to shivering. Feeling cold in labour also predisposes to shivering, which in turn leads to a further rise in temperature.

The incidence of shivering or tremors has been reported in association with E-series prostaglandins in early canine studies, before the synthesis of misoprostol. In early animal models investigating the ability of prostaglandin E_1 to inhibit gastric acid secretion, one of its important reported side effects was trembling, in addition to rhinorrhoea, emesis, diarrhoea and cardiovascular changes. These side effects, along with its short duration of action, all limited its therapeutic use at that time (Collins *et al.*, 1985). Prostaglandin E_1 is known to raise body temperature by mediating the febrile response of thermoregulation centers in the brain. Even minute quantities of E-series prostaglandins have been reported to produce a sharp rise in body temperature when directly injected into the brain substance of unanaesthetised animals (Milton and Wendlandt, 1971; Veale & Cooper, 1975).

The main action of E-series prostaglandins is its cytoprotective role on the gastric mucosa (Bauer, 1985; Dajani, 1987). Other actions involve the circulatory system, where they cause an increase in cardiac output and vasodilatation of vascular beds, and intestinal smooth muscle by shortening transit time, which leads to diarrhoea, nausea, vomiting, and abdominal cramps. All the actions of E-series prostaglandins are also demonstrated by its synthetic analogue Misoprostol, which is known to exert its effect mainly on the gastrointestinal tract and the uterus. Consequently, the adverse effects of therapeutic doses of Misoprostol primarily involve these two systems, such as diarrhoea, nausea, vomiting, and uterine contractions, which lead to expulsion of uterine contents.

Misoprostol is generally associated high acceptability and a low incidence of side effects (Tables 5.16 & 5.17). In abortion and mid-trimester termination of pregnancy studies using misoprostol, the reported incidence of nausea ranged from 5% (Creinin, 1994) to 70% (Schaff *et al.*, 1995), that of vomiting ranged from 5% (Creinin, 1994) to 44% (El-Refaey, 1995 a), and that of diarrhoea ranged from 7% to 50% (Thong & Baird, 1992; Creinin *et al.*, 1997). It appears that the highest frequencies of side effects have been reported by El-Refaey *et al.*, whether in early abortion (1994 a, b; 1995 a) or mid-trimester termination of pregnancy studies (1993; 1995 b).

Pyrexia has also been reported as a direct effect to misoprostol, both with therapeutic doses (Haberal *et al.*, 1996; El-Refaey *et al.*, 1995 a; Creinin *et al.*, 1997 b; Jain & Mishell, 1994; Srisomboon *et al.*, 1997 b), and with overdosage (Graber & Meier, 1991; Bond & Van-Zee, 1994; Austin *et al.*, 1997). It appears that the incidence of misoprostol-associated side-effects increase the higher the dosage administered. The reported incidence of vomiting, for example, is 10% with a 400 μgm oral dose of misoprostol (Aubeny & Baulieu, 1991), which increases to 40% with an 800 μgm oral dosage (El-Refaey & Templeton, 1994 b).

The most common known side effects of misoprostol are gastrointestinal (Tables 5.14 & 5.15). Aubeny *et al.* (1995) investigated an oral 400 μgm dosage of misoprostol for induction of early abortion, after pretreatment with 600 mg of mifepristone in a multicenter trial that included 1,108 women. The most common side-effects reported were moderate uterine cramps (80.5%) and gastrointestinal symptoms (34.9%); especially vomiting (18.3%) and diarrhoea (10.5%). In another study comparing the efficacy of 400 μgm of oral misoprostol with 800 μgm vaginally administered misoprostol for early

abortion (Creinin *et al.*, 1997 a), vomiting was reported in 30% and 13%, and diarrhoea in 50% and 38%, respectively.

Thong and Baird (1992) investigated the clinical efficacy of 600 μgm of oral misoprostol administered 48 hrs. after 200 mg of mifepristone for induction of early abortion. Vomiting occurred in 24% and diarrhoea in 7% of women following misoprostol administration. Baird *et al.* (1995) compared 600 μgm of oral misoprostol with 0.5 mg gemeprost (cervagem) following mifepristone for induction of early abortion. The incidence of nausea and vomiting after misoprostol (47.8 and 21.9% respectively) was significantly higher (p-value < 0.001) than after gemeprost (33.9 and 12% respectively).

El-Refaey & Templeton (1994 b) compared the use of a single dose of 800 μgm of oral misoprostol, or divided into two sequential doses of 400 μgm administered two hours apart, after pre-treatment with 200 mg of mifepristone, in a randomised controlled study of early abortion. Gastrointestinal side effects occurred more frequently among women receiving the single oral dose; vomiting in 40%, nausea in 68%, and abdominal pain in 36%, compared to 31%, 59% and 39%, respectively, among those receiving the sequential regimen, but the differences were not statistically significant. Diarrhoea occurred in 33% of women receiving the single higher dose, compared to 21% in the second group, and was significantly higher both in incidence (p-value = 0.049) and severity (p-value = 0.034).

Shivering was not known to be a side effect to misoprostol prior to using it in the third stage of labour. Studies investigating the use of oral misoprostol in the treatment of peptic ulcer have not reported this side effect (Dajani *et al.*, 1991 b; Dajani & Agrawal, 1995). The use of single oral misoprostol doses of up to 800 μgm (El-Refaey & Templeton, 1994; El-Refaey *et al.*, 1995 a;

Lawrie *et al.*, 1996), daily doses of up to 2400 μgm (Carbonell *et al.*, 1997), and total daily doses of up to 2200 μgm for a period up to 3 months (Herting & Nissen, 1986; Data sheet compendium, 1993) were not associated with shivering. Our study demonstrates that shivering is a genuine side effect of misoprostol. There are indications that shivering might also be dose-dependent (Hofmeyr *et al.* 1998).

Shivering was not reported with the use of 800 μgm of misoprostol in abortion and termination of pregnancy studies, but was only detected when the drug was used postpartum. It may be questioned whether the occurrence of shivering was an idiosyncratic reaction in some individuals, which could be verified by studying the same women who shivered after giving them increasing dosages of the drug in the non-pregnant condition, if possible.

In our study, a significant rise in temperature is seen within the first 15 minutes after delivery, even before the onset of shivering, which may suggest a pyrogenic effect to misoprostol as a direct action of the drug. Whether this is true, however, needs to be investigated more thoroughly in a larger study. A second significant rise in temperature also occurs shortly after the onset of visible shivering. Pyrexia was therefore found to occur both before and after the shivering episode. Whether, in fact, there are two peaks to the rise in temperature or whether the rise in temperature is continuous, remains unascertained due to our small sample size, and needs to be verified. Its biological significance, if true, remains to be elucidated in further works.

Despite the fact that the same percentage of patients received epidural in labour in the two groups, and that the frequency of shivering in labour was similar in the two groups, there was a high incidence of shivering after delivery among women receiving epidural in the misoprostol group, such that

all the women who had epidural in labour shivered after delivery. Epidural analgesia is known to impair thermoregulatory control, induces redistribution hypothermia (Negishi *et al.*, 1996), and increases the incidence of shivering between 33% and 66% (Brownridge, 1986). The mechanism by which shivering occurs in association with epidural analgesia is thought to be thermogenic (Scherer, 1997). Following induction of epidural anaesthesia, core temperature declines as a result of internal redistribution of body heat from the core thermal compartment to peripheral tissues. Lowered core body temperatures leads to peripheral thermoregulatory vasoconstriction to slow the loss of heat. This is followed by shivering, which raises body temperature by increasing muscle tone and oxygen uptake. Brownridge (1986) conducted a prospective survey to determine the incidence and severity of shivering and associated risk factors among 200 women receiving epidural analgesia in labour. Shivering occurred in 50% of the patients soon after the initial dose of Bupivacaine, and was more common among those who had experienced shivering in labour before epidural, and those who had received nitrous oxide (p-value < 0.005). Shiverers were more likely to feel cold after delivery than non-shiverers (p-value < 0.001), but, on the whole, shivering was regarded by patients as a minor symptom.

In the misoprostol group, pyrexia was significantly associated with receiving epidural anaesthesia in labour (p-value< 0.001). Although the pathophysiology of rise in temperature in association with epidural analgesia in labour remains hypothetical, it is thought that epidural analgesia reduces the loss of heat, through sweating and hyperventilation, which is also surpassed by labour-induced heat production (Mercier & Benhamou, 1994). However, 2 hours after delivery, the mean temperature remained significantly higher than that measured before delivery by about 1.2°C (p-value < 0.001). We expect that after this time period the effect of the epidural, which could have contributed

to the rise in temperature, would have worn off. This proves that the rise in temperature is a genuine side effect of oral misoprostol in the third stage of labour. However, there are many questions unanswered. There must be additional mechanisms that go into play with regards to the occurrence of shivering and pyrexia in association with oral misoprostol administration in the third stage of labour.

A clear association was found between shivering and the rise in temperature in the misoprostol group (p-value < 0.001), such that the incidence of pyrexia among shiverers was 60%, compared to none (0%) among the non-shiverers (p-value < 0.001). In the "other oxytocics" group, none of those who shivered developed pyrexia (p-value = 1.0). In the misoprostol group, all the women (100%) who had received epidural analgesia shivered, compared to 53% among those who did not have epidural. In contrast, the shivering rate in the "other oxytocics" group was the same regardless of whether women received epidural analgesia in labour or not. Among women receiving "other oxytocics", there was a much smaller percentage of shiverers and the duration of shivering was much shorter. Shivering in this group might have occurred due to a surge in catecholamines or due to excitement.

Analgesics for after-pains were required more often among women receiving oral misoprostol (47%) than among those receiving "other oxytocics" (30%), but the difference was not statistically significant. This finding has been reported in several other studies, and has been attributed to uterine pain as a result of the strong contractile effect misoprostol exerts on the uterus (Baird *et al.*, 1995; Schaub *et al.*, 1995; Aubeny *et al.*, 1996).

Statistical analysis proved that patients were similar at entry into the study. However, it appears that women recruited to the misoprostol group had a

longer duration from rupture of membranes to delivery, and from epidural to delivery than those receiving "other oxytocics" (Table 5.2). This difference although not significant, could not be explained. One of the limitations of this study is its small sample size. It was quite difficult to get mothers to agree to participate in a study that necessitated the measurement of temperature at frequent intervals for three further hours after delivery, and which required the continuous presence of the researcher, at a time when most of them were anxious to rest.

Observer bias could not be eliminated due to non-blinding of the researcher to the hypothesis under investigation. However, this was minimised by adhering to the precise time required for temperature measurement, and obtaining accurate readings by means of an electronic thermometer. It is quite unlikely that the sizeable difference in the incidence of shivering among women receiving oral misoprostol compared to those receiving other oxytocics could be an artefact of an anticipated side effect. This is especially so if we also consider the association between shivering and the more objective measure of rise in temperature.

Another source of bias lies in the subjective evaluation of cold sensation by the mothers, whether in labour or after delivery. Furthermore, the severity of shivering was not assessed since it was not objective to assess it in the scope of this study. Furthermore, all measurements in this study have been made in relation to the exact time of delivery, which was thought to be the most appropriate parameter since the exact time of drug administration was not documented, but was considered to have taken place after delivery of the anterior shoulder or within 2 to 5 minutes of delivery for both study groups.

Results of this study demonstrate that oral misoprostol administration in the third stage of labour is associated with a significantly high incidence of pyrexia within a few minutes of drug administration, and a significantly high incidence of shivering. Another significant rise in temperature occurs after the onset of shivering. Epidural analgesia in labour also contributes to the high incidence of shivering and pyrexia among mothers receiving oral misoprostol in the third stage of labour. Further research is needed to understand the interplay between pyrexia and shivering, and to identify methods to overcome these side effects.

Table 5.1: Comparison of baseline characteristics of women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study

Demographic characteristics	Misoprostol n=32	Other oxytocics n=30	p-value
Mean (SD) maternal age (yrs.)	30 (4.9)	29 (6.3)	0.16
Parity: No. (%) Primiparous No. (%) Multiparous	16 (50) 16 (50)	10 (33) 20 (67)	0.24
Mean (SD) gestation at delivery (wks.)	40 (1.2)	40 (1.3)	0.34

Table 5.2: Comparison of labour and delivery variables of women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study

Events in labour	Misoprostol n=32	Other n=30	p-value
Labour variables:			
No. (%) spontaneous onset of labour	23 (72)	17 (57)	0.29
No. (%) induction of labour	9 (28)	13 (43)	0.29
No. (%) SROM	15 (47)	10 (33)	0.31
No. (%) ARM	17 (53)	20 (67)	0.31
No. (%) augmented with syntocinon	8 (25)	7 (23)	1.00
No. (%) epidural analgesia	17 (53)	15 (50)	1.00
Interval from rupture of membranes to delivery (hours:mins)	6:06 (4:57)	4:15 (3:01)	0.08
Interval from start of epidural to delivery (hours:mins)	6:07 (3:02)	4:26 (1:54)	0.07
Length of labour*:			
Length of labour (hours:mins)	7:46 (5:0)	6:25 (3:29)	0.22
Length of 1st stage (hours:mins)	6:33 (4:30)	5:08 (3:10)	0.16
Length of 2nd stage (hours:mins)	1:30 (1:14)	1:08 (0:47)	0.19
Length of 3rd stage (mins.)	6 (3)	7 (4)	0.35

SROM: Spontaneous Rupture of Membranes
ARM: Artificial Rupture of Membranes
* Values are Mean (SD)

Table 5.3: Comparison of events and side effects after the third stage of labour among women receiving Misoprostol or Other oxytocics in the pyrexia and shivering study

	Misoprostol n = 32 No. (%)	Other oxytocics n = 30 No. (%)	p-value
Nausea	10 (31)	12 (40)	0.60
Vomiting	1 (3)	2 (7)	0.61
Antiemetic administration	0	4 (13)	0.05*
Analgesics for after-pains	15 (47)	9 (30)	0.20

Table 5.4: Comparison of Cold sensation in labour and after delivery, and the frequency of shivering among women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study

Side effects	Misoprostol n=32	Other n=30	p-value
No. (%) epidural analgesia	17 (53)	15 (50)	1.0
Cold and shivering in labour:			
No. (%) cold & shivery in labour	7 (22)	6 (20)	0.86
No. (%) cold & shivery before epidural	2 (6)	2 (7)	0.95
No. (%) cold & shivery after epidural	7 (22)	6 (20)	0.90
Cold and shivering after delivery:			
No. (%) cold after delivery	13 (41)	10 (33)	0.56
No. (%) experiencing shivering	25 (78)	4 (13)	<0.001*
Mean time interval from delivery to start of shivering (mins.)	18 (12.7)	14 (10.4)	0.60
Median time interval from delivery to start of shivering (mins.)	15 (10-24)	20 (2-20)	0.91
Mean (SD) duration of shivering (mins.)	33 (22.0)[a]	8 (4.8)[b]	0.02*
Median (IQR) duration of shivering (mins.)	30 (20-35)	10 (5-10)	<0.01*

a. Longest duration of shivering was 115 min.
b. Longest duration of shivering was 12 min.

Table 5.5: Comparison of the association of cold sensation and shivering after delivery between both study groups in the pyrexia and shivering study

	Shivering No. %	No Shivering No. %	p-value
Misoprostol			
Cold sensation	12 (92.3)	1 (7.7)	0.20
No cold sensation	13 (68.4)	6 (31.6)	
Other Oxytocics			
Cold sensation	4 (40.0)	6 (60.0)	0.008*
No cold sensation	0	20 (100.0)	

Table 5.6: Comparison of the frequency of shivering among women receiving Misoprostol or Other oxytocics controlling for epidural analgesia in the pyrexia and shivering study

	Misoprostol No. %	Other oxytocics No. %	p-value
No epidural			
Shivering	8 (53)	2 (13)	0.02*
No shivering	7 (47)	13 (87)	
Epidural			
Shivering	17 (100.0)	2 (13)	0.00*
No shivering	0	13 (87)	

Table 5.7: Comparison of the incidence of pyrexia among women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study

Incidence of pyrexia	Misoprostol n=32	Other n=30	p-value
No. (%) Pyrexia	15 (47)	4 (13)	0.001*
Mean (SD) time from delivery to rise in temperature (min.)	33 (11)	45.0 (12)	0.05
Median (IQR) time from delivery to rise in temperature (min.)	30 (30-45)	45 (34-56)	0.20

Table 5.8: Temperature measurements before and after drug administration among women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study (data are presented as means and SD)

	Misoprostol n=32 Temp°C (SD)	Other oxytocics n=30 Temp°C (SD)	p-value
Temp. on admission	36.4 (0.40)	36.5 (0.33)	0.21
Temp. before delivery	36.4 (0.37)	36.5 (0.28)	0.12
At 15 min. after delivery	37.1 (0.60)	36.6 (0.44)	<0.001*
At 30 min. after delivery	37.1 (1.92)	36.7 (0.50)	0.25
At 45 min. after delivery	37.8 (0.90)	36.7 (0.53)	<0.001*
At 60 min. after delivery	37.7 (0.93)	36.7 (0.55)	<0.001*
At 2 hrs. after delivery	37.6 (0.84)	36.6 (0.48)	<0.001*
At 3 hrs. after delivery	37.4 (0.67)	36.5 (0.43)	<0.001*

Table 5.9: Comparison of changes in temperature before and after drug administration among women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study (data are presented as means and SD)

	Misoprostol		Other oxytocics	
	Mean change temp°C (SD)	p-value^{p}	Mean change temp°C (SD)	p-value^{p}
From before delivery to 1 hr. after delivery	1.3 (0.9)	<0.001*	0.2 (0.6)	0.11
From before delivery to 15 min after delivery	0.7 (0.6)	<0.001*	0.08 (0.4)	0.33
From 15 min. to 30 min. after delivery	0.03 (1.8)	0.93	0.06 (0.2)	0.14
From 30 min. to 45 min. after delivery	0.7 (1.7)	0.04*	0.03 (0.2)	0.55
From 45 min. to 60 min. after delivery	-0.02 (0.2)**	0.75	-0.003 (0.2)	0.94
From 60 min. to 2 hrs. after delivery	-0.2 (0.6)	0.05*	-0.1 (0.3)	0.15
From 2 hrs. to 3 hrs. after delivery	-0.2 (0.5)	0.01*	-0.05 (0.2)	0.15

P-value^{p} = P-value for paired sample t-test
** Minus sign (-) indicates fall in temperature

Table 5.10: Difference in mean rise in temperature between women receiving Misoprostol or Other oxytocics in the third stage of labour in the pyrexia and shivering study (data are presented as means and SD)

	Temp°C	95% CI
At 15 min. after delivery	0.5	0.19 to 0.72
At 30 min. after delivery	0.4	0.3 to 1.13
At 45 min. after delivery	1.0	0.66 to 1.41
At 60 min. after delivery	1.0	0.64 to 1.41
At 2 hrs. after delivery	0.9	0.61 to 1.32
At 3 hrs. after delivery	0.8	0.55 to 1.21

Table 5.11: Comparison of the frequency of pyrexia among women who had epidural anaesthesia in the Misoprostol or Other oxytocics groups

	Epidural No. %	No Epidural No. %	p-value
Misoprostol			
Pyrexia	11 (64.7)	4 (26.7)	< 0.05*
No Pyrexia	6 (35.3)	11 (73.3)	
Other Oxytocics			
Pyrexia	4 (26.7)	0	0.1
No Pyrexia	11 (73 .3)	15 (100.0)	

Table 5.12: Comparison of the frequency of pyrexia among women who shivered in the Misoprostol or Other oxytocics groups

	Pyrexia No. %	No Pyrexia No. %	p-value
Misoprostol			
Shivering	15 (60.0)	10 (40)	< 0.001*
No shivering	0	7 (100)	
Other Oxytocics			
Shivering	0	4 (100)	0.41
No shivering	4 (15.4)	22 (84.6)	

* F-test of interaction between shivering and randomised group on the change in temperature = 7.2, p-value < 0.001.

Table 5.13: Difference in mean change in temperature between shivering and non-shivering patients in the Misoprostol group

	Difference in temperature °C	95% CI
15 minutes of delivery	0.5	0.1 to 0.9
30 minutes of delivery	0.4	0.6 to 1.3
45 minutes of delivery	1.1	0.7 to 1.6
60 minutes of delivery	1.4	0.9 to 1.8
2 hrs. of delivery	0.9	0.2 to 1.6
3 hrs. of delivery	0.7	0.1 to 1.4

Table 5.14: Comparison of the association of shivering and pyrexia in relation to epidural analgesia among women in the Misoprostol and Other oxytocics groups

	Pyrexia No. %	No Pyrexia No. %	p-value
MISOPROSTOL			
Epidural			
Shivering	11 (65)	6 (35)	NC
No shivering	0	0	
No Epidural			
Shivering	4 (50)	4 (50)	0.04*
No shivering	0	7 (100)	
OTHER OXYTOCICS			
Epidural			
Shivering	0	2 (100)	0.38
No shivering	4 (31)	9 (69)	
No Epidural			
Shivering	0	2 (100)	NC
No shivering	0	13 (100)	

NC = Not computed

Table 5.15 Incidence of pyrexia and shivering among women receiving postpartum analgesia in the Misoprostol versus Other oxytocics groups

	Misoprostol No. %	Other Oxytocics No. %	p-value
Shivering	12 (80.0)	1 (11.0)	0.002*
No shivering	3 (20.0)	8 (89.0)	
Pyrexia	6 (40.0)	1 (11.0)	0.20
No Pyrexia	9 (60.0)	8 (89.0)	

Table 5.16. Side effects of misoprostol reported in studies of early abortion

Author (year)	Misoprostol dose & route of administration	Nausea	Vomit.	Diarrh.	Abd. pain	Fever
Thong & Baird (1992)	600 μgm orally	-	24%	7%	-	-
Creinin & Vittinghoff (1994)	800 μgm vaginally	5%	5%	18%	-	-
El-Refaey & Templeton (1994 b)	800 μgm single oral dose Vs. two doses of 400 μgm sequentially 2 hrs. apart	68% 59%	40% 31%	33% 21%	36% 39%	- -
Schaff *et al.* (1995)	800 μgm vaginally	70%	23%	46%	-	-
Aubeny *et al.* (1995)	400 μgm orally + extra 200 μgm if conceptus not expelled after 3 hrs.	-	18.3%	10.5%	80.5%	-
Baird *et al.* (1995)	600 μgm orally	47.8%	21.9%	-	-	-
El-Refaey *et al.* (1995 a)*	800 μgm orally Vs. 800 μgm vaginally	70% 60%	44% 31%	36% 18%	- -	- -
Creinin *et al.* (1997 a)	400 μgm orally Vs. 800 μgm vaginally	- -	30% 13%	50% 38%	- -	- -
Creinin *et al.* (1997 b)	800 μgm vaginally	33%	18%	18%	-	31%

Vomit.: Vomiting
Diarrh.: Diarrhoea
Abd.pain: Abdominal pain

* The following side effects were also reported:
Among women receiving the 800 μgm dosage orally: Hot flushes in 46%, tiredness in 67%, headache in 22%, dizziness in 41%.
Among women receiving the 800 μgm dosage vaginally: Hot flushes in 49%, tiredness in 70%, headache in 21%, dizziness in 44%.

Table 5.17. Side effects of misoprostol reported in studies of mid-trimester termination of pregnancy

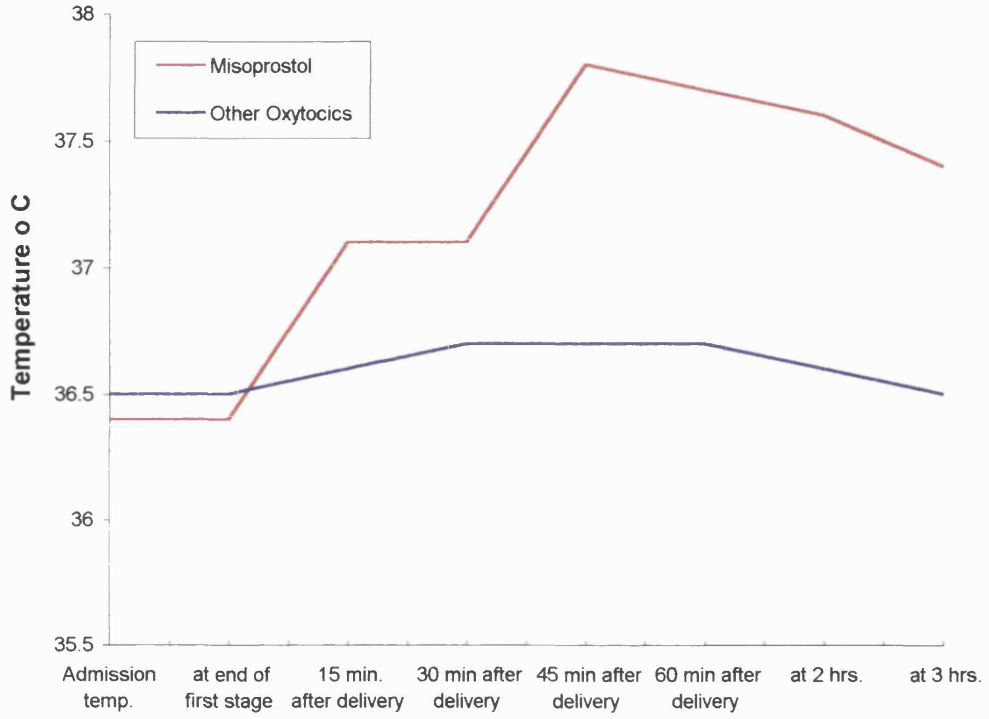
Author (year)	Misoprostol dose & route of administration	Nausea	Vomit.	Diarrh.	Abd. pain	Fever
El-Refaey *et al.* (1993)	400 μgm orally 3 hourly, up to 3 doses followed by Gemeprost vaginally	-	37%	20%	-	-
Jain & Mishell (1994)	200 μgm vaginally every 12 hrs.	-	4%	4%	57%	11%
El-Refaey & Templeton (1995 b)	600 μgm vaginally followed by 400 μgm vaginal doses every 3 hrs.	-	57%	29%	-	-
	Vs. 600 μgm vaginally followed by 400 μgm oral doses every 3 hrs.	-	61%	35%	-	-
El-Refaey *et al.* (1995 a)	800 μgm vaginally followed by 400 μgm oral doses every 3 hrs.	50%	40%	20%	-	45%
Jain & Mishell (1996)	200 μgm vaginally every 12 hrs with or	-	8.6%	2.8%	65.7%	14.3%
	without intracervical laminaria	-	6.1%	0%	57.6%	3.0%
Ho et al.* (1996)	400 μgm orally for a maximum of 5 doses	32%	52%	56%	100%	-
Wong *et al.*** (1996)	400 μgm orally followed 12 hrs later by Gemeprost	8.6%	8.6%	8.6%	34.3%	-
Srisomboon *et al.* (1997 b)	200 μgm intracervico-vaginally every 12 hrs.	6%	6%	2%	-	8%
Batioglu *et al.* (1997)	200 μgm orally, to be repeated hourly up to 1200 μgm	14.3%	14.3%	28.6%	16.7%	-

Vomit.: Vomiting
Diarrh.: Diarrhoea
Abd.pain: Abdominal pain

* Also reported dizziness in 28%, fatigue in 52%, breast tenderness in 28%, headache in 28%.

** Also reported dizziness in 2.9%, fatigue in 2.9%, breast tenderness in 2.9%.

Figure 5.1. Comparison of temperature changes before delivery and after drug administration between women receiving Misoprostol or Other oxytocics in the third stage of labour



Appendix 5.A: Data collection sheet for pyrexia and shivering study

Patient details: *(affix a sticker or write)*

Hospital number.....Date.....
Patient Surname.....Ethnic origin.....
Forename.....Parity.....
DOB.....Gestation.....

Labour & Delivery:

Spontaneous / Induced
Prostin Yes / No
Oxytocin Yes / No

Membranes:
SROM / ARM Date & Time .....

Epidural:
Yes / No Date & Time .....

Dose & Mixture used .....

Top up: 1. Time.....:.....Dose.....Mixture 1.....
2. Time.....:.....Dose.....Mixture 1.....
3. Time.....:.....Dose.....Mixture 1.....
4. Time.....:.....Dose.....Mixture 1.....

Was patient cold in labour? Yes / No

If receiving epidural, was patient cold,
before epidural? Yes / No
after epidural? Yes / No
both? Yes / No

Time fully dilated .....:.....

Time started pushing .....:..... Length of first stage: .....:.....

Delivery time baby .....:..... Length of first stage: .....:.....

Delivery time placenta .....:..... Length of first stage: .....:.....

Third stage:

Drug used:
Misoprostol / Other .....

Side effects:
Nausea Yes / No
Vomiting Yes / No
Shivering Yes / No
Pyrexia Yes / No

Other drugs administered:
Antiemetic Yes / No
Analgesic Yes / No
Other .....

Cold & Shivering after the third stage:

Was patient cold after delivery? Yes / No

Shivering episode Yes / No

Began:.....:.....

Ended:.....:.....

Temperature measurements:

	Time	Temperature	Pulse
On admission	.....:.....	.....	.....
End of first stage	.....:.....	.....	.....
First hour after delivery			
15 min.	.....:.....	.....	.....
30 min.	.....:.....	.....	.....
45 min.	.....:.....	.....	.....
60 min.	.....:.....	.....	.....
Post delivery *(May be recorded in postnatal ward)*			
2 hrs.	.....:.....	.....	.....
3 hrs.	.....:.....	.....	.....

Chapter 6

The use of rectally administered Misoprostol for the treatment of postpartum haemorrhage.

Background

Misoprostol is rapidly absorbed after oral or vaginal administration, appearing in the blood in significant concentrations within 2 minutes, and producing an equally rapid uterotonic effect (Karim, 1987; Gaud & Connors, 1992; Zieman *et al.*, 1997). The fact that misoprostol absorption appears to occur directly from the mucous membranes (Karim, 1987), suggests that its absorption is mucous-membrane dependent, which predicts that its absorption from the rectal mucosa may be just as effective.

Experience gained with Misoprostol while evaluating its use in the third stage of labour led us to consider that it may be effective in the treatment of PPH due to uterine atony. The rectal route of administration has obvious advantages in PPH patients, since women under general anaesthesia or those who become comatose due to excessive loss of blood, cannot be given oral medication, and any drug administered vaginally in the presence of heavy vaginal bleeding is unlikely to be effective. The rectal route of administration therefore appears ideal. It is the least invasive route, compared to other drugs that have to be administered intravenously or intramyometrially.

Uterine atony is the most common cause of primary PPH (Weekes & O'toole, 1956), resulting in 40% of hysterectomies performed to control bleeding (Clark *et al.*, 1984). Given that up to one-fifth of maternal cardiac output, which is in excess of 600 mL/min, enters the uteroplacental circulation at term, it is understandable that atonic PPH can be rapidly fatal. When the diagnosis of uterine atony as the cause of blood loss is established, treatment is started by the administration of 20 units of oxytocin (syntocinon) in 1000 mL of Ringer Lactate

or Normal Saline intravenously, at a rate of approximately 10 mL (200 mU) of oxytocin per minute. This is done simultaneously with vigorous uterine massage to provoke contraction of the uterus. If the uterus does not respond to oxytocin infusion and uterine massage, methylergonovine (Methergine 0.2 mg IM) may be administered. This produces strong tetanic uterine contractions, in addition to end-artery constriction that persists for several hours. However, when intramuscularly administered, its absorption from muscle may be unpredictable, especially when peripheral perfusion is diminished as a result of the drop in blood pressure associated with excessive blood loss. On the other hand, intravenous administration of Methergine causes a sharp rise in blood pressure. Ergot derivatives are contraindicated if the patient is hypertensive or haemodynamically unstable, and nowadays are used much less frequently as a result of their association with coronary artery spasm, myocardial infarction, postpartum cerebral angiopathy and stroke (Barinagarrementeria *et al.*, 1992; Taylor & Cohen, 1985; Nall & Feldman, 1998).

Because of their strong uterotonic features, prostaglandins play a major role in the treatment of PPH due to uterine atony (Corson & Bolognese, 1977; Toppozada *et al.*, 1981; Hayashi *et al.*, 1984; Jain *et al.*, 1986), and are recognised to be superior to both oxytocin and ergometrine in this respect. Prostaglandin analogues were found to be more potent than their parent compounds. Prostaglandins $PGF_{2\alpha}$, PGE_2, and their analogues have all been successfully used to control atonic PPH, using various routes of administration. Sulprostone (PGE_2 analogue) has been successfully used to control atonic PPH both intravenously and intramuscularly (Laajoki & Kivikoski, 1986). Continuous irrigation of the uterine cavity with a low concentration of PGE_2 has been reported to be effective in controlling severe PPH with minimal side effects (Peyser *et al.*, 1990). The efficacy of the

intramyometrial injection of $PGF_{2\alpha}$ in the treatment of PPH has also been reported (Jacobs & arizas, 1979; Toppozada, 1986). Intravenous PGE_2 (Sarkar & Mamo, 1990), and intrauterine gemeprost pessaries (Barrington & Roberts, 1993; El-Lakani & Harlow, 1994) have all been used to control PPH due to uterine atony. However, vaginally administered PGE_2 pessaries were reported to be unsatisfactory in controlling bleeding, since the drug is likely to be expelled (Hertz *et al.*, 1980).

In the mid-1980's, the 15-methyl derivative of prostaglandin $F_{2\alpha}$ (Carboprost tromethamine; Hemabate™, Upjohn, Michigan, USA), was developed and approved for the treatment of uterine atony. It is more potent than its parent compound, and has a longer duration of action. Carboprost is effective with both intramyometrial (Jacobs & arizas, 1979; Toppozada, 1986) or intramuscular administration (Toppozada, 1986). However, the intramuscular route has been reported as the most effective route of administration (Toppozada, 1986). The initial recommended dosage is 250 μgm (0.25 mg) administered intramuscularly, to be repeated if necessary at 15 to 90 minute intervals, up to a maximum of eight doses. Peak blood levels are reached between 15 to 60 minutes of intramuscular injection. Carboprost is effective in treating 60 to 85% of patients with uterine atony unresponsive to oxytocin and standard therapy, with an overall success rate of 95% (Toppozada *et al.*, 1981; Hayashi *et al.*, 1984; Buttino & Garite, 1986).

Prostaglandin F_2 analogues, however, have several disadvantages. They degenerate under the influence of light and heat, and must therefore be protected from light and kept refrigerated at 4°C. Administration must be parenteral, which is an invasive procedure that carries the risk of infection. The intra-myometrial route of administration carries a theoretical risk of organ damage, or of bleeding

from the puncture site on the uterus. These drugs are also expensive, making them unaffordable to most developing countries. Furthermore, patients receiving Carboprost should be carefully monitored. Its side effects include a 10 to 25% incidence of gastrointestinal symptoms, such as diarrhoea and vomiting, a 5% incidence of pyrexia, in addition to flushing and tachycardia in about 20% of cases. Carboprost belongs to prostaglandins of the F group, and as such are bronchoconstrictors. Their use in patients with asthma is potentially hazardous, and they can cause dyspnoea in non-asthmatic patients. Other potentially serious side effects include elevated blood pressure and pulmonary oedema. Carboprost is therefore contraindicated in women with cardiovascular or pulmonary disease because of its potential hypertensive and bronchoconstrictor effects (Hankins *et al.*, 1988).

If all medical measures to control haemorrhage fail, surgical treatment becomes inevitable, by embolisation or ligation of the internal iliac artery or, as a last resort, hysterectomy.

The efficacy of rectally administered misoprostol in the prevention of PPH was confirmed by the reports of Bamigboye *et al.* (1998 a, b). Their first study (Bamigboye *et al.*, 1998 a) was a randomised controlled trial, comparing rectally administered misoprostol with syntometrine for management of the third stage of labour among low risk women. Women were randomised to receive either 400 μgm of misoprostol rectally (n = 241) or syntometrine 1 ampoule IM (n = 250). The two groups were found to be similar in terms of length of the third stage and postpartum blood loss. In their second study (Bamigboye *et al.*, 1998 b) women were randomly allocated to receive either 400 μgm of misoprostol rectally (n = 271) or placebo (n = 275) for management of the third stage of labour.

Postpartum blood loss of ≥ 1000 mL occurred in 4.8% of the misoprostol group, and in 7% of the placebo group. Further oxytocic administration to enhance uterine contractility was required for 1.8% of the misoprostol group, and 4.4% of the placebo group.

We were therefore encouraged to investigate the efficacy of misoprostol in controlling bleeding in cases of atonic PPH, unresponsive to current first-line therapy. At present there are no publications comparing misoprostol to other conventional remedies used for the treatment of PPH. The aim of this study is to demonstrate that misoprostol may play a role in the treatment of atonic PPH.

Patients and methods

While investigating the effect of oral misoprostol on uterine contractility in the immediate postpartum period (chapter 2), at The National University Hospital in Singapore, the results were encouraging, and it was decided to investigate the uterine response when misoprostol was administered by the rectal route. However, due to limitations of time, this route of administration was tested in only one patient, using the same methodology described in chapter 2. A dosage of 500 μgm of misoprostol was administered through the rectal route to a parturient woman, with an uneventful obstetric and pregnancy history and normal labour, after physiological delivery of the placenta. Table 6.1 demonstrates the increase in mean active pressure from 475 mm.Hg in the control pre-stimulation period before drug administration, to 1024 mm.Hg within the first 30 minutes of administration. Figure 6.1 shows the output from the sonicaid monitor

demonstrating intrauterine pressure changes before and after administration of 500 μgm of misoprostol rectally.

This study is an observational study investigating the use of rectally administered misoprostol in the treatment of postpartum haemorrhage. Women were delivered and treated at the Obstetric Hospital, UCH, over an 18-month period. Fourteen women received rectal misoprostol, and 18 received carboprost (Hemabate). The carboprost cases are reported here for comparison purposes, and do not represent a control group.

The hospital protocol for treatment of PPH involves resuscitation, exclusion of traumatic bleeding, administration of oxytocin by intravenous bolus (10 - 20 units) and infusion (40 units in 500 mL normal saline over 15 minutes), and ergometrine (0.5 - 1.0 mg, either intravenously or intramuscularly), in addition to bimanual uterine compression. If bleeding persists despite this management, carboprost is given.

Among women receiving rectal misoprostol, initial management of all the 14 cases was similar and followed the hospital protocol, which was adhered to in ten women. However, in the other four women ergometrine was contraindicated because of preeclampsia. When bleeding continued in spite of this treatment, carboprost was requested by the attending obstetrician. While awaiting carboprost, misoprostol 1000 μgm (five tablets) was administered rectally. If carboprost was ready for administration before misoprostol, it was administered according to hospital policy. Although when first testing the efficacy of rectal misoprostol on postpartum uterine contractility, we used a 500 μgm dosage, we opted, however, to double this dosage (1000 μgm) when using this route for the

treatment of atonic PPH in this study, since we were faced with an emergency situation and a quick uterine response was urgently needed.

Carboprost (Hemabate) was administered to 18 women who did not have contraindications to carboprost; such as hypertension, asthma, pulmonary oedema or diabetes. Among women receiving carboprost, management of all the cases was similar and followed the hospital protocol.

Results

During the 18-month study period there was a total of 201 PPH cases. Table 6.2. demonstrates some demographic characteristics and causes of PPH among this group. PPH due to uterine atony was seen in 129 women (64%), PPH associated with retained products of conception was seen in 86 women (43%), and due to genital tract trauma in 34 women (17%). Among women with atonic PPH, haemorrhage was arrested in 169 women (84%) using conventional oxytocics; syntometrine, syntocinon, or ergometrine, depending on maternal condition. The other 32 women (16%) required additional prostaglandins to control the haemorrhage. Rectal misoprostol was administered to 14 women, and carboprost was administered to 18 women.

Table 6.3 demonstrates a comparison between the estimated blood loss, need for blood transfusion and units required among women who received rectal misoprostol and those who received Carboprost. Maternal age, gestation, and method of delivery were comparable between the two groups. Among women who received rectal misoprostol, the median estimated blood loss was 1000 mL

(Range 500 - 2000 mL, IQR = 875 – 1425 mL). Nine women (64%) had blood loss estimated at 1000 mL or more. Eleven of the 14 women (79%) required blood transfusion (median = 2 U, range 0 – 4 U, IQR = 1.5 – 2.5 U). Among women who received carboprost, the median estimated blood loss was 1250 mL (Range 700 – 4500 mL, IQR = 787 – 1850 U). Thirteen women (72%) had blood loss estimated at 1000 mL or more, and 14 women (78%) required blood transfusion (median = 2 U, range 0 – 5 U, IQR = 1.5 – 4 U). The differences between the two groups were not statistically significant.

Table 6.4 demonstrates the obstetric details, estimated blood loss, and treatment of the 14 women who received 1000 μgm of misoprostol rectally. In all 14 women, haemorrhage was controlled, and sustained uterine contraction was quickly achieved. No further uterotonic treatment was required in any of the 14 patients, and no side effects were reported. Patients number 3, 11, and 14 lost 1700, 1500, and 2000 mL, respectively. In these three patients, disseminated intravascular coagulopathy (DIC) developed, and was diagnosed within an hour of delivery (prolonged coagulation times, decreased fibrinogen, and increased fibrin degradation products). Treatment included transfusion with blood, fresh frozen plasma, platelets, and cryoprecipitate. Two of these patients (11 and 14) required admission to the intensive therapy unit overnight. All women made a full recovery.

Table 6.5 demonstrates the obstetric details, estimated blood loss, and treatment of the 18 women who received Carboprost. Haemorrhage was controlled, and sustained uterine contraction was quickly achieved in all cases. No further uterotonic was required and no side effects were reported. Two patients, numbers

7 and 17 developed disseminated intravascular coagulopathy (DIC), and were appropriately treated. All made a full recovery.

Discussion

Most obstetric units nowadays have a standard protocol for the management of atonic PPH. The principal first-line treatment is intravenous ergometrine, with or without supplementary oxytocin by intravenous infusion. If bleeding continues, a parenteral prostaglandin such as carboprost is indicated. However, currently used drugs for treatment of severe atonic PPH have their limitations. Oxytocin and ergometrine often fail to control major PPH. Ergometrine can also cause vomiting and a rise in blood pressure; therefore it is contraindicated in women with hypertension or preeclampsia. It is also an emetic, which is a relative contraindication when general anaesthesia is used.

The second line of management in women who continue to bleed, in spite of treatment with oxytocin and ergometrine, is parenteral prostaglandins. The place of parenteral prostaglandins such as Carboprost in the treatment of intractable PPH is now well established (Toppozada *et al.*, 1981), and is generally the preferred pharmacological agent when oxytocin is unsuccessful. However, they have several disadvantages; they require parenteral administration, which carries the risk of infection, in addition to other potentially serious side effects such as hypertension, dyspnoea, pulmonary oedema, and exacerbation of asthma. Parenteral prostaglandins also require special storage conditions and refrigeration, and are also expensive, which makes them unaffordable to most developing countries.

This study suggests that rectally administered misoprostol may be a useful addition to the range of therapeutic interventions currently available for the treatment of PPH. Administration of misoprostol is quick and non-invasive, its absorption is rapid, and it is associated with minimal side effects. In particular, it does not cause a rise in blood pressure (El-Refaey & Templeton, 1994 b), and is therefore a potential alternative to ergometrine in hypertensive patients.

Carboprost belongs to prostaglandins of the F group, and as such are bronchoconstrictors. Misoprostol, on the other hand, is a prostaglandin E1 analogue, and as such has a relaxing effect on bronchial smooth muscle. In fact, there are indications that misoprostol may be useful for the management of bronchial asthma (Shield, 1995). It would therefore seem a safer alternative to Carboprost in the management of atonic PPH in women with asthma or pulmonary oedema. In addition, the drug has the advantage of being inexpensive.

Among women who received rectal misoprostol in this study, ergometrine was contraindicated in four patients because of high blood pressure. Both the second and the sixth patients in particular, had additional complications. The second patient had four relative contraindications to carboprost: hypertension, asthma, pulmonary oedema and diabetes. The sixth patient also had a medical history of bronchial asthma, along with Mitral valve prolapse and regurgitation, and had been admitted into hospital during pregnancy with a severe asthma attack. Both these women were effectively treated with misoprostol, avoiding the potential side effects associated with ergometrine and prostaglandin F_2 analogues.

Although we used a 500 μgm dosage when first testing the efficacy of rectal misoprostol on postpartum uterine contractility, we opted to double this dosage

(1000 μgm) when using this route for the treatment of atonic PPH. Since we were faced with an emergency situation, we did not want to take a chance with continuation of haemorrhage, and a quick uterine response was urgently required. This dosage, however, was used with great caution because of the concern with hyperpyrexia. In the intrauterine pressure study (chapter 2), there was one patient who developed hyperthermia after administration of an 800 ugm oral misoprostol dosage. However, she was the only patient who developed this severe reaction in all our series of studies, and the possibility remains that this hyperthermia was an idiosyncratic reaction to oral misoprostol in this particular patient. Although a rise in temperature has been reported as a direct effect to therapeutic doses of misoprostol (Haberal *et al.*, 1996; El-Refaey *et al.*, 1995 a; Creinin *et al.*, 1997 b; Jain & Mishell, 1994; Srisomboon *et al.*, 1997 b), hyperthermia (temperature of 41.1°C or above) has never been reported in abortion studies or in the field of gastroduodenal ulcer (Dajani *et al.*, 1991; Lanza *et al.*, 1991; Herting & Nissen, 1986), and has only been reported in cases of misoprostol toxicity or overdosage using very high doses of the drug (Graber & Meier, 1991; Bond & Van-Zee, 1994; Austin *et al.*, 1997).

It may be that rectal misoprostol could be used routinely as an alternative to parenteral prostaglandins in the treatment of intractable PPH. Misoprostol might replace carboprost or at least minimise the number of women requiring this invasive treatment. Women with intractable PPH unresponsive to oxytocin and ergometrine, or those who have contraindications to carboprost, may respond to rectal misoprostol; and it may be that such women should be given misoprostol before resorting to more invasive surgical procedures.

The implications for the use of misoprostol in the treatment of refractory PPH worldwide are significant. Among the 14 cases who received rectal misoprostol in this study, misoprostol was used as an alternative to both ergometrine and carboprost. Neither of these drugs is widely available in developing countries because of their specific storage requirements, which also make them unaffordable. Misoprostol has the potential to become an alternative to ergometrine for first-line management of PPH, and may also be an effective alternative for treatment of PPH in women who have contraindications to prostaglandin F_2 analogues, such as those with asthma and cardiovascular or pulmonary disease.

Although this is an observational study, and the data presented here are limited, they are promising and potentially important. The data for women who received carboprost are presented for comparison purposes only, and does not represent a control group. It showed, however, that rectally administered misoprostol may be similar in efficacy to carboprost in resolving atonic PPH. Further analytical studies are required to compare between the efficacy of rectal misoprostol and carboprost in the treatment of atonic PPH.

Furthermore, since there was no control group it is difficult to ascertain with a high degree of accuracy whether the observed effects on contraction of the uterus and the resolution of PPH was the effect of misoprostol alone. The possibility cannot be ruled out that these women responded to the oxytocics previously administered as first line therapeutic agents, or to the combined additive effects of these oxytocics and misoprostol, rather than to the misoprostol alone.

The extent of absorption of misoprostol is highly variable depending on its route of administration, and is known to be significantly highest with oral intake. However, in the preliminary stages of this study, we assumed that the absorption and pharmacokinetics of rectally administered misoprostol mirror those for vaginal administration, since there has been no published data addressing the pharmacokinetics of rectal misoprostol. Karim (1987) reported that the absorption of misoprostol is very rapid, such that it is detected in the circulation within two minutes of oral ingestion, reaching peak plasma levels in less than 15 minutes. Neto *et al.* (1988) investigated uterine activity patterns after administration of 200 and 400 μgm of misoprostol orally, and 200 μgm vaginally in women with intrauterine fetal death at term, and reported that onset of uterine activity in response to misoprostol varied between 10 to 120 min. of drug administration. Peak serum levels of misoprostol are reached between 60 and 120 min. of vaginal administration, in contrast to the oral route, which is much faster; plasma levels peaking between 12.5 and 60 min. of administration (Zieman *et al.*, 1997).

In our series of studies, the response to oral misoprostol was seen to be very rapid, strong uterine contractions being achieved within a few minutes. The brisk clinical response observed after rectal administration in this study suggests that the pharmacokinetics of rectal misoprostol may be very close to that of oral misoprostol. A more critical step to evaluate the potential efficacy of rectal misoprostol for the treatment of PPH, would be to identify its absorption and pharmacokinetics with rectal administration.

The availability of a cheap and effective alternative to ergometrine and parenteral prostaglandins for the treatment of atonic PPH would be a major advantage to both developing and developed countries. There is considerable potential for

misoprostol to reduce maternal mortality from PPH in developing countries that cannot afford parenteral prostaglandins, since it is inexpensive, and is therefore affordable to most countries.

Figure 6.1: Output from the sonicaid monitor demonstrating IUP recording before and after administration of 500 μgm of misoprostol rectally

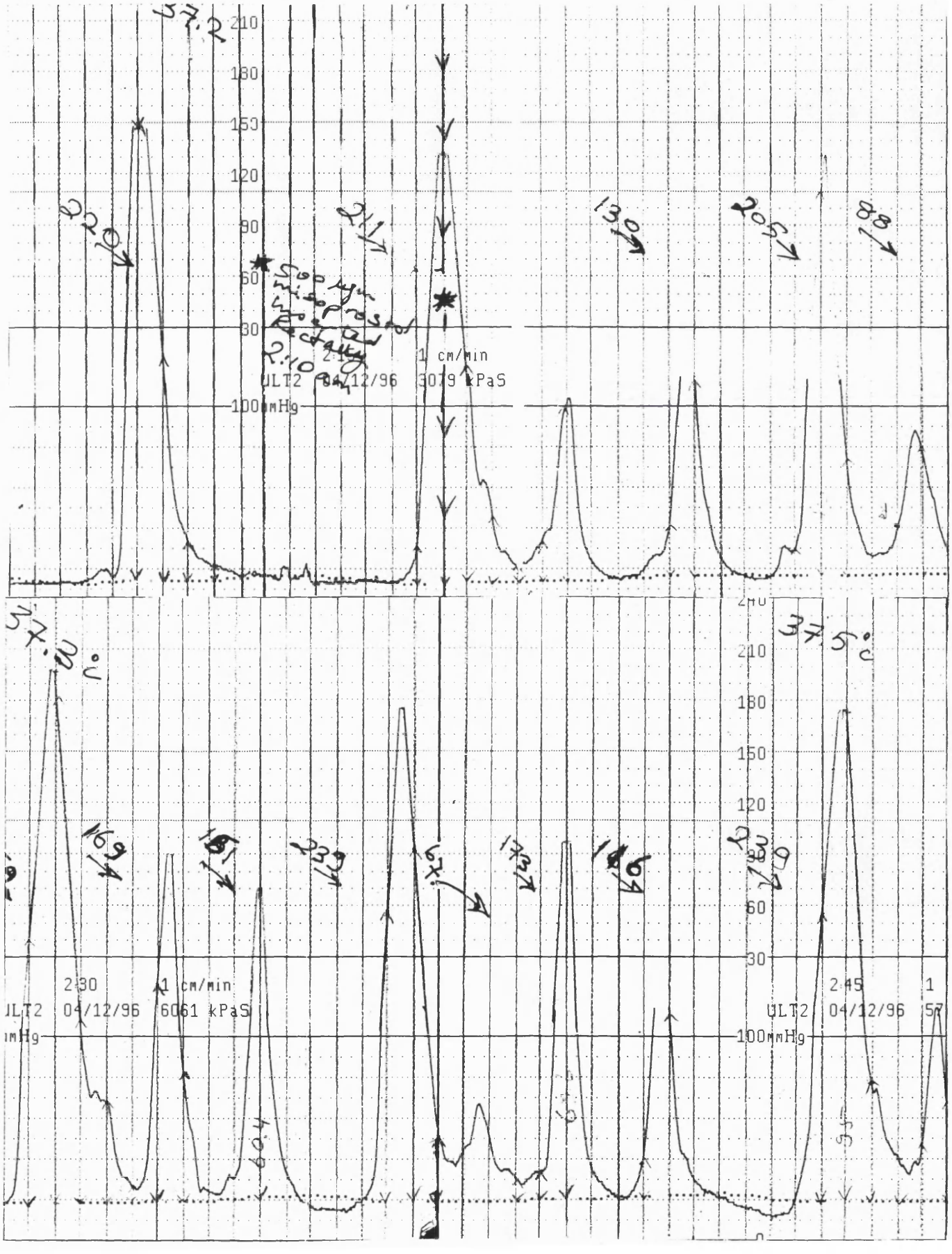


Table 6.1: Mean uterine activity before and after administration of 500 μgm of misoprostol rectally

Interval	Mean uterine activity (mm.Hg)
Pre-stimulation period (before drug administration)	476
First 30 min. after administration	1024
30 – 60 min. after administration	799
60 – 90 min. after administration	452

Table 6.2: Demographic characteristics, method of delivery and causes of PPH and estimated blood loss among study population

	n = 201
Median Maternal age (IQR)	30 (25.8 – 34)
Median Gestation (IQR)	40 (39 – 41)
Causes of PPH:	
No. (%) Uterine atony*	129 (64%)
No. (%) Retained products of conception or MROP**	86 (43%)
No. (%) Genital tract trauma	34 (17%)
Estimated Blood Loss (mL):	
500 - < 1000	136 (68%)
1000 - < 2000	48 (24%)
2000 & above	17 (8.5%)
No (%) requiring blood transfusions	67 (33%)
Median Blood Units (IQR)	3 (2 - 4)

* 34 of the women with uterine atony also had retained products of conception, and 5 had accompanying bleeding due to genital tract trauma.

** 10 of the women with MROP had accompanying bleeding due to genital tract trauma.

Table 6.3: Estimated blood loss and need for blood transfusion among women who received rectal misoprostol and those who received Carboprost (Hemabate)

	Misoprostol	Carboprost	P-value*
Median Maternal age (IQR)	33 (26 – 40)	31 (27 – 35)	0.4
Median Gestation (IQR)	40 (38 – 41)	40 (38 – 41)	0.9
Method of delivery:			
Spontaneous vaginal delivery	9 (64.3%)	8 (44.4%)	0.6
Ventouse	2 (14.3%)	3 (16.7%)	
Forceps	0	1 (5.6%)	
Caesarean section	3 (21.4%)	6 (33.3%)	
Estimated Blood Loss (mL):			
500 - < 1000	5 (35.7%)	5 (27.8%)	0.4
1000 - < 2000	8 (57.1%)	9 (50.0%)	
2000 & above	1 (7.1%)	4 (22.2%)	
Median Estimated Blood Loss	1000 (875 – 1425)	1250 (787 – 1850)	0.4
No (%) requiring blood transfusions			
Median Blood Units (IQR)	2.0 (1.5 – 2.5)	2.0 (1.5 – 4)	0.6

* Non normally distributed continuous variables were compared by Mann-Whitney test, and categorical varables were compared by Chi-square testing or Fisher's exact test as appropriate.

Table 6.4: Obstetric details, estimated blood loss, and treatment of women receiving 1000 μgm of misoprostol rectally

No.	Parity	Age (Y)	Gest. (wks)	Complication	Mode of delivery	Uterotonic used	EBL	Bld. Transf.
1	1	24	40	Preeclampsia	SVD	O (b)	500	0
2	3	34	38	DM, Preeclampsia, bronchial asthma	Em. LSCS	O (iv)	800	4 U
3	2	43	24	Abruption, DIC	Vag. breech	O (b,iv), E	1700	4 U
4	1	32	41	Retained placenta	Ventouse	O (b,iv), E	700	0
5	0	28	38	Failed induction	Em. LSCS	O (b,iv), E	1000	2 U
6	1	26	40	Asthma, mitral vlv. prolapse, IUGR	SVD	O (b,iv), E	1400	2 U
7	0	38	39	None	SVD	O (b,iv), E	900	2 U
8	1	21	41	None	SVD	O (b,iv), E	1200	2 U
9	0	29	39	Preeclampsia	Ventouse	O (b,iv)	1000	2 U
10	4	40	39	Preeclampsia	SVD	O (b,iv)	1100	2 U
11	1	33	40	DIC	SVD	O (b,iv), E	1500	2 U
12	5	41	38	None	SVD	O (b,iv), E	1000	2 U
13	1	28	40	None	SVD	O (b,iv), E	700	0
14	1	31	39	Breech, DIC	El. LSCS	O (b,iv), E	2000	4 U

Gest. = Gestation
EBL = Estimated blood loss
Bld. Transf. = Blood transfusion
SVD = Spontaneous vaginal delivery (Cephalic)
O (b) = Oxytocin by intravenous bolus
O (iv) = Oxytocin by intravenous infusion
DM = Diabetes Mellitus
Em. LSCS = Emergency Lower segment caesarean section
El. LSCS = Elective Lower segment caesarean section
DIC = Disseminated intravascular coagulopathy
E = Ergometrine
IUGR = Intrauterine growth restriction

Table 6.5: Obstetric details, estimated blood loss, and treatment of women receiving Carboprost

No.	Parity	Age (Y)	Gestation (wks)	Complication	Mode of delivery	EBL	Blood Transfusion
1	1	36	38	None	Em.LSCS	3000	4 U
2	1	25	35	APH, Abruption	Em.LSCS	1800	4 U
3	1	28	38	None	SVD	700	0
4	0	19	39	None	SVD	800	0
5	0	34	40	None	Forceps	1000	2 U
6	0	26	41	None	Ventouse	800	2 U
7	1	23	39	DIC	SVD	1500	4 U
8	2	39	37	Retained placenta	SVD	1000	2 U
9	1	31	40	None	SVD	1000	0
10	1	32	42	None	SVD	1500	2 U
11	0	31	42	None	Ventouse	900	4 U
12	0	33	39	None	Ventouse	700	0
13	2	35	41	Breech	El. LSCS	1500	2 U
14	1	35	37	Oligohydramnios, Twins, failed IOL	Em.LSCS	1500	2 U
15	1	34	41	None	SVD	2500	3 U
16	1	29	40	Failed IOL	Em.LSCS	4500	5 U
17	0	27	40	DIC	SVD	1000	2 U
18	0	27	37	APH, Abruption	Em.LSCS	2000	4 U

APH = Antepartum haemorrhage
EBL = Estimated blood loss
SVD = Spontaneous vaginal delivery (Cephalic)
Em. LSCS = Emergency Lower segment caesarean section
El. LSCS = Elective Lower segment caesarean section
DIC = Disseminated intravascular coagulopathy

Chapter 7

Summary and conclusions

Postpartum haemorrhage is one of the leading causes of maternal mortality and morbidity over the world, and is estimated to account for 28% of maternal deaths in developing countries. One of the few interventions that holds some hope of success in reducing maternal deaths due to postpartum haemorrhage is through the use of an appropriate oxytocic agent for prophylaxis against excessive blood loss.

The currently used oxytocics in the form of ergometrine-containing preparations are associated with several problems; they are contraindicated in hypertension in pregnancy, frequently cause nausea and vomiting, and require administration by intramuscular injection, which is an important consideration in the era of hepatitis and AIDS. Furthermore, their instability at high temperatures and special storage requirements make them unsuitable for use in temperate climates, and is an important obstacle to their widespread use in the developing world.

The search for an effective, easily stored, affordable uterotonic agent for the prevention of PPH is therefore of utmost importance. The availability of an oral and thermostable preparation for routine management of the third stage of labour will have considerable effects on obstetric practice and maternal morbidity and mortality in both industrialised and developing countries.

The concept of using misoprostol as a prophylactic agent for management of the third stage of labour and prevention of PPH arose from its confirmed uterotonic properties and their application in various obstetric conditions. Other advantages to misoprostol include its rapid absorption after oral ingestion, and its thermostability. It is well tolerated, has few side effects, and does not cause a rise in blood pressure, therefore it can be used by all

parturient women. Furthermore, misoprostol has the advantage of being inexpensive, and is therefore affordable to most countries.

The most important advantage to misoprostol is its potential to be used enterally. Its oral administration means that it may be given in suboptimal hygienic circumstances without the need for sterile needles and syringes, which is an important public health consideration.

Postpartum uterine contractility in response to different doses of oral misoprostol:

The physiological intrauterine pressure study was conducted to investigate the response of the uterus in the puerperal state to orally administered misoprostol. Oral misoprostol doses of 800, 600, 500, 400, and 200 μgm were investigated. Orally administered misoprostol in the immediate postpartum period showed a fast onset (median = 7.2 min., IQR of 4.7 to 10.8 min.), and a prolonged duration of action (median = 65 min., IQR of 57.5 to 75.0 min.), which is of special clinical relevance in the third stage of labour. The shortest onset and longest duration of action was achieved with the 800 μgm oral misoprostol dosage.

Misoprostol was found to induce a highly significant increase in mean uterine contractility, irrespective of the dosage used. Doses as small as 200 μgm were shown to have a uterotonic effect. However, no statistically significant difference was found in mean uterine contractility among the five dosage groups. The highest increase in uterine activity was achieved with the 600 μgm oral misoprostol dosage, followed by the 500 μgm dosage.

Side effects observed with oral misoprostol were mild. The two most obvious side effects were shivering and pyrexia. The highest incidence of side effects was seen with the 800 μgm dosage, such as shivering, pyrexia, nausea, and dizziness. The 600 μgm dosage induced the highest change in uterine contractility, but was also associated with a high incidence of shivering and pyrexia. The 500 μgm dosage was associated with strong uterine contractility and moderate side effects.

Clinical studies identifying the efficacy and side effects of different dosages of oral misoprostol in the third stage of labour:

The appropriate effective misoprostol dosage, associated with the least side effects, that could safely and ethically be used in a randomised trial needed to be determined. This was implemented by means of two consecutive observational pilot studies. The first pilot study investigated the efficacy of 600 μgm of orally administered misoprostol in the management of the third stage of labour and prevention of PPH. Its main objective was to investigate the PPH rate and the associated clinical effects of this dosage. The second pilot study examined the PPH rate and perceived incidence of side effects in two further groups of women receiving two lower oral misoprostol doses; 400 μgm and 500 μgm. The three groups were then compared.

Oral misoprostol used prophylactically in the third stage of labour was associated with a lower PPH rate, less need for further therapeutic oxytocics, and shorter length of the third stage than those reported with physiological management, and were comparable to results obtained with syntometrine (Keirse *et al.*, 1995). The percentage of patients with an estimated blood loss ≥ 500 mL was lowest among women in the 600 μgm group (6%), compared to 8% in those receiving 500 μgm, and 12% in the 400 μgm group, but the

differences were not statistically significant. The efficacy of oral misoprostol in lowering postpartum blood loss may well be dose-dependant. The group receiving the 600 μgm oral misoprostol dosage showed a significantly lower mean blood loss, lower mean length of the third stage, and less patients required additional therapeutic oxytocics than the other two groups, but was associated with a higher incidence of side effects. A non-significant reduction in both systolic and diastolic blood pressure and a significant rise in temperature were noted with the three dosages. Women receiving the 600 μgm, 400 μgm, and 500 μgm doses experienced a significant rise in temperature of 0.5°C, 0.6°C, and 0.7°C respectively. Gastrointestinal side effects were infrequent, mild, and did not require any treatment. A clear difference was found among the three groups in their perception of shivering, being reported by 41% of patients receiving the 400 μgm dosage, against 62% among those receiving the 500 μgm and the 600 μgm dosages.

The results of both pilot studies imparted that misoprostol may be an effective agent, associated with few side effects, that can be used for prophylactic management of the third stage of labour and prevention of PPH. It was then decided to conduct a randomised controlled clinical trial to ascertain the efficacy of oral misoprostol by comparing it to other currently used oxytocics in the prophylactic management of the third stage of labour.

The randomised controlled trial examining the efficacy and side effects of oral Misoprostol versus other oxytocics in active management of the third stage of labour:

In the randomised trial we decided to investigate the efficacy and side effects of oral misoprostol in comparison with the established practice of prophylactic management of the third stage of labour in the U.K. We wanted to find out

whether active management of the third stage of labour could be carried out safely with oral misoprostol, and to determine whether, in terms of maternal morbidity, it is justifiable to use misoprostol in place of the current policy that involves using syntometrine, syntocinon, or ergometrine. The primary aim of this randomised trial was to ascertain whether the use of 500 μgm of oral misoprostol could replace this policy, without an increase in the incidence of PPH. The secondary aim was to assess the incidence and severity of the side effects associated with each policy. Women were randomised to receive either 500 μgm of oral misoprostol immediately after delivery of the baby and clamping and division of the cord, or the standard policy of "other oxytocic agents", i.e. syntometrine, syntocinon, or ergometrine, depending on maternal condition.

The PPH rate was 12% in the misoprostol arm, and 11% in the "other oxytocics" arm, but the difference was not statistically significant. The median blood loss, the proportions of women requiring manual removal of the placenta and blood transfusion, and the length of the third stage of labour were all comparable between the two randomised arms. The percentage of women requiring further oxytocic administration was slightly higher in the misoprostol arm, but this difference was not statistically significant.

A statistically significant increase in mean temperature of about 0.6°C was seen in the misoprostol arm, in comparison to an increase of only 0.3°C in the "other oxytocics" arm. This difference was statistically significant. A slight fall in systolic blood pressure was also noted in the misoprostol arm (mean change of –1.3 mm.Hg), in comparison to a small increase in the "other oxytocics" arm (mean change of +0.1 mm.Hg), but the difference was not statistically significant. Both arms showed a comparable small reduction in diastolic blood pressure, haemoglobin concentration and haematocrit levels.

Shivering and rise in temperature were the main side effects of oral misoprostol. Shivering occurred twice as often in the misoprostol arm compared to the "other oxytocics" arm, and this difference was statistically significant. The incidence of shivering was significantly higher among women who had received epidural analgesia in the misoprostol arm. Pyrexia was the second side effect, the incidence of which was significantly higher in the misoprostol arm. A clear association was found between shivering and pyrexia.

Misoprostol was better tolerated than the "other oxytocics" in terms of the incidence of nausea, headache, and dizziness, although the difference in the incidence of other gastrointestinal side effects, such as vomiting, abdominal pain, or diarrhoea was not statistically significant.

The randomised trial showed that orally administered misoprostol was as effective as injectable oxytocics in terms of the incidence of PPH and blood loss during and after delivery. This suggests that a policy using oral misoprostol for management of the third stage of labour is a safe and simple alternative to the current policies that use injectable oxytocics.

Pyrexia and shivering among parturient women following administration of oral Misoprostol versus Other oxytocics for management of the third stage of labour:

Misoprostol is generally associated high acceptability and a low incidence of side effects. While the randomised controlled trial was in progress, the high incidence of shivering and rise in temperature among women receiving oral misoprostol prompted us to investigate further into their occurrence. Patients

in this study were recruited from women who had given consent to participate in the third stage randomised controlled trial.

This study confirmed that oral misoprostol administered in the third stage of labour was associated with a significantly high incidence of shivering and pyrexia. Shivering occurred within 5 to 58 minutes of delivery, starting within a mean time of 18 min. (SD = 13, median = 15 min., IQR of 10 to 24 min.), and its mean duration was 33 min. (SD = 22.0, median = 30 min., IQR of 20 to 35 min.). The mean time interval from delivery to rise in temperature was 33 minutes. Shivering was significantly associated with pyrexia among women receiving oral misoprostol. A significant rise in temperature was obvious within the first 15 minutes of delivery, followed by a second significant rise occurring shortly after the onset of visible shivering. Both shivering and pyrexia were seen to occur more often among women who had received epidural analgesia in labour. However, further research is needed to understand the interplay between pyrexia and shivering, and to identify methods to overcome these side effects.

The use of rectally administered Misoprostol for the treatment of postpartum haemorrhage:

The therapeutic value of Misoprostol was also tested in the treatment of PPH due to uterine atony using the rectal route of administration, which has obvious advantages with vaginal bleeding. The aim of this study was to demonstrate that misoprostol may play a role in the treatment of PPH due to uterine atony. A dosage of 1000 μgm of rectally administered misoprostol induced a quick uterine response and cessation of haemorrhage. Misoprostol may therefore be a useful addition to the range of therapeutic interventions

available for the treatment of PPH, avoiding the potential side effects associated with ergometrine and prostaglandin F_2 analogues.

The series of studies described in this thesis prove that oral misoprostol may be effectively used for the prevention of PPH, and possibly for the treatment of atonic PPH. Their main weakness lies in the method of assessment of postpartum blood loss. A major problem that faced us with these studies was in accurate determination of the most important outcome variable; postpartum blood loss. Discrepancies among reports of PPH rates occur as a result of the different methods used for blood loss measurement, whether quantitatively or visually (Newton *et al.* 1961; Brant, 1967; Razvi *et al.*, 1996). However, subjective estimation of blood loss in parturient women is still the most common method applied in the UK. Major studies in the literature investigating management of the third stage of labour have also used subjective assessment of blood loss to report rates of PPH. In line with other landmark papers (Nieminen & Jarvinen, 1963; Dumoulin, 1981; Prendiville *et al.*, 1988; Begley, 1990; McDonald *et al.*, 1993; Mitchell & Elbourne, 1993; Khan *et al.*, 1995; Yuen *et al.*, 1995), we also employed clinical assessment of blood loss. However, because this assessment is subjective, surrogate and objective indices of blood loss were also recorded, including the need for blood transfusion, use of other therapeutic oxytocics, length of the third stage, and whether manual removal of the placenta was performed. We also attempted to record changes in haemoglobin and haematocrit concentration before and after delivery. Any delayed haemorrhage within the first 24 hours was also documented. All of the above constitute the main outcome measures of the studies included in the third stage reviews of The Cochrane Library (McDonald *et al.*, 1998; Prendiville *et al.*, 1998).

These studies, however, are not the end-point of misoprostol research. Although misoprostol has great potential as a routine prophylactic agent in the third stage of labour, further studies are required. The dosage and route of administration that confer maximum efficacy with minimum side effects are yet to be determined. There is room to examine smaller dosages, and other routes of administration of misoprostol, e.g. rectally, for prophylaxis against PPH. The pharmacokinetics of rectally administered misoprostol should be investigated. The use of Misoprostol in the third stage of labour may also be further tested by a double-blind randomised controlled trial. Future research should also aim at quantitative measurement of postpartum blood loss in association with misoprostol use in the third stage of labour. Furthermore

The World Health Organisation is currently conducting a large multicenter double-blind randomised controlled clinical trial on 20,000 women in 10 countries, comparing orally administered misoprostol to oxytocin (10 IU) for routine management of the third stage of labour, aiming to collect adequate information on the safety and side effects of misoprostol.

Misoprostol may well be the perfect agent for use in both industrialised countries and the developing world. It has great potential to reduce maternal mortality due to PPH. The implications are considerable, since if the use of oral misoprostol becomes standard practice, the management of the third stage of labour will be simpler, potentially safer and more acceptable to women and their attendants over the world.

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