STUDIES WITH AN ANTI PROGESTERONE IN EARLY AND MIDTRIMESTER PREGNANCY.

Mary Wallace Rodger, MB ChB., MRCOG.,

DEDICATION.

“To my father

John Campbell Rodger

1925 - 1998.”
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Declaration.

The contents of this thesis have not been submitted elsewhere for any other degree, diploma or professional qualification.

The thesis has been composed by myself and I have been responsible for patient recruitment, clinical management and laboratory studies, unless otherwise acknowledged.

Mary W Rodger
1998.
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Abbreviations.

The following abbreviations have been used in the text of this Thesis.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>3βHSD</td>
<td>3β hydroxy steroid dehydrogenase.</td>
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<td>cm</td>
<td>centimetre.</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid.</td>
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<td>g/dl</td>
<td>gramme per decilitre.</td>
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<td>GABA</td>
<td>Gamma-aminobutyric acid.</td>
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<td>hCG</td>
<td>human chorionic gonadotrophin.</td>
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<td>HSP-90</td>
<td>Heat Shock Protein-90.</td>
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<td>IP₃</td>
<td>Inositol triphosphate.</td>
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<td>IU</td>
<td>International Units.</td>
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<td>IUCD</td>
<td>Intrauterine contraceptive device.</td>
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<td>KD</td>
<td>KiloDalton.</td>
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<td>kg</td>
<td>kilogramme.</td>
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<td>M</td>
<td>Molar.</td>
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<td>MU</td>
<td>Montevideo Unit.</td>
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<td>mg</td>
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<td>mmHg</td>
<td>millimetres of mercury.</td>
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<td>mU/min</td>
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<td>m V</td>
<td>milli Volt.</td>
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<td>ng</td>
<td>nanogramme.</td>
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<td>NHS</td>
<td>National Health Service.</td>
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<td>PG</td>
<td>prostaglandin.</td>
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<td>PGDH</td>
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<td>PGI₂</td>
<td>prostacyclin.</td>
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<td>RNA</td>
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<td>μg</td>
<td>microgramme.</td>
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<td>WHO</td>
<td>World Health Organization.</td>
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<td>%</td>
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"I was so struck by the sight of the table where they were lifting the woman, I did not say a word. It looked like some awful torture table, with those metal stirrups sticking up in mid-air at one end and all sorts of instruments and wires and tubes I couldn't make out properly at the other".


"RU 486..........the moral property of women".

Abstract.
Vacuum aspiration is the most commonly used method of pregnancy termination in the United Kingdom. Although it is a safe technique it requires the use of skilled medical and nursing staff and is most effective when performed under general anaesthesia. Before eight weeks of amenorrhoea, most spontaneous abortions are complete and surgical evacuation of the uterus is unnecessary. If suitable agents are used to induce abortion before this time, termination of pregnancy should be possible without resort to surgery.

Prostaglandin E analogues effectively induce early abortion but their usefulness is limited by a high incidence of prostaglandin-related side effects such as vomiting, diarrhoea and pain. The antigestagen, mifepristone, causes few side effects but a high incidence of incomplete abortion makes it unsuitable as an early abortifacient. The combination of mifepristone and prostaglandin couples the efficacy of the latter with the acceptability of the former, providing a potential medical alternative to vacuum aspiration. In this thesis safety, efficacy and acceptability of early medical abortion with mifepristone and the prostaglandin analogue gemeprost are investigated in Chapters 2, 3 and 5. In Chapter 4 the mechanism of abortion with these agents is explored.

The use of a single dose of 400 mg, 500 mg or 600 mg of mifepristone followed 48 hours later by a half or a whole 1 mg gemeprost pessary was shown to induce complete abortion in 95% of women of ≤ 56 days amenorrhoea. No significant differences were demonstrated between the three treatment regimes. When 600 mg of mifepristone was given with either a half or a whole gemeprost pessary, women receiving the smaller dose of prostaglandin experienced significantly less severe pain. Abortion rates were not compromised by a reduction in the dose of prostaglandin with 98% of women receiving a half pessary aborting, compared with 100% of women receiving a whole pessary. Pretreatment with mifepristone or gemeprost 48 hours prior to the administration of 1 mg gemeprost was also studied. Measurement of uterine tone with an intrauterine pressure catheter showed that while pretreatment with gemeprost had no effect on uterine tone following a further dose of gemeprost, pretreatment with mifepristone exerted a significant effect. In addition, the pattern of uterine activity following gemeprost or mifepristone pretreatment was shown to differ.
Blood loss was measured during and after the induction of abortion with mifepristone and gemeprost in 222 consecutively treated women of <63 days of amenorrhoea. The median loss <56 days amenorrhoea was 72 mls. Blood loss was found to increase with increasing gestation and was significantly greater in women treated between 56 and 63 days of amenorrhoea.

Although the introduction of prostaglandins to gynaecological practice has improved midtrimester abortion techniques, it remains a long, unpleasant and relatively high risk procedure. In Chapter 6 the effects of pretreatment with 600 mg mifepristone on induction of midtrimester abortion with gemeprost pessaries were studied in 100 women of between 12 and 18 weeks of pregnancy in a double blind, randomised placebo trial. Significantly more women pretreated with mifepristone aborted within 24 hours of prostaglandin administration (94% versus 80% receiving placebo) and the prostaglandin induction-abortion interval was only 6.8 hours following mifepristone pretreatment compared with 15.8 hours after placebo. Analgesic requirements were significantly reduced by antigestagen pretreatment as was the length of stay in hospital.

In summary, the combination of mifepristone and prostaglandin analogue is a safe, effective and acceptable method of abortion when restricted to the first 56 days of amenorrhoea. The smallest effective dose of antigestagen or prostaglandin, however, is not yet known. In addition, the mechanism of action of mifepristone in its induction of uterine activity is not fully understood. Mifepristone pretreatment in the second trimester of pregnancy significantly reduces the prostaglandin induction-abortion interval.
CHAPTER 1.

LITERATURE REVIEW.
An estimated 30 to 40 million legal and as many illegal abortions are performed globally each year (Tietze & Henshaw, 1986), with the greatest use of abortion as a means of fertility control being made by countries with poor provision or ineffective forms of contraception (Tietze & Lewit, 1981). Maternal morbidity and mortality as a consequence of abortion, both legal and illegal, is incalculable. However, with a projected 30% increase in the number of fertile women in the developing world by the year 2000, the statement that "Universal access to safe abortion could undoubtedly save the lives of a million or more women in the 1990s" is both pertinent and obvious (Potts & Rosenfield, 1990). Developed countries which have legal provision of abortion have been rewarded by a continued reduction in mortality rates for abortion. Between 1971 and 1981 in the United States the abortion mortality rate fell 16-fold (Gastaadt, 1986). In the United Kingdom only nine deaths have been attributed directly to the 1,541,399 abortions performed between 1985 and 1993, representing a rate of 5.8 deaths per million therapeutic abortions (Department of Health, 1996).

Abortion, certainly in Europe and the United States, seems to be a relatively safe procedure but the risk of major complications associated with abortion remains at between 1 and 2% (Cates & Grimes, 1981; Franks, 1985). The most important risk factor for any abortion is the gestational age at which the pregnancy is terminated. Morbidity associated with abortion increases with advancing gestational age and the risk of major complications rises by 15 to 30% for every week of delay after eight weeks gestation (Cates & Grimes, 1981). The earlier an abortion is performed, the greater the potential for minimising both major and minor complications.

In Scotland, as well as the rest of Europe and the United States, the majority of abortions are performed in the first 12 weeks of pregnancy. Of the 11,143 pregnancies terminated in 1995 in Scotland, 94% were terminated in the first trimester and 63% before 10 weeks (Scottish Office, Department of Health, 1996).

**Vacuum Aspiration.**

Vacuum aspiration is the safest method of surgical termination of first trimester pregnancy (JPSA/CDC, 1976; Tietze & Lewit, 1972) and appears to have no long-term effects on reproductive health (Frank et al, 1987; WHO, 1979). Complications of the procedure are lowest when it is performed between seven and 10 weeks gestation (Tietze & Lewit, 1972) by a skilled operator (Cates & Grimes, 1981), under general anaesthesia (Tietze & Lewit, 1972). Complications are significantly increased at all gestations if local anaesthesia is used (Tietze & Lewit, 1972) and it has
been estimated that up to 25% of women undergoing vacuum aspiration under 12 weeks with a local anaesthetic will require additional sedation (in some cases inhalational anaesthesia) to allow completion of the procedure (Rovinsky, 1971).

Vacuum aspiration without general anaesthesia is best tolerated by women at earlier gestations when evacuation of the uterus can be attained by the use of a small diameter suction curette (Goldsmith & Margolis, 1971; Landesman et al, 1973). However, it has been shown that complications, in particular incomplete evacuation, are more frequent before six weeks gestation when compared with vacuum aspiration at 7 to 10 weeks gestation (Tietze & Lewit, 1972). A failure rate of as high as 11 to 13% has been reported by several authors for early vacuum aspiration under local anaesthesia (Hodgson, 1977; Atienza et al, 1975; Smith & Baird, 1980).

General anaesthesia may well enable the provision of a better tolerated, less complicated and more effective vacuum aspiration but, in the developing world, paucity of finance and skilled personnel limits its availability - and it must be borne in mind that 29% of abortion-related deaths in the United States between 1972 and 1985 were attributed to the use of general anaesthesia (Atrash et al, 1988).

Common complications of vacuum aspiration such as uterine perforation, haemorrhage, infection, anaesthetic mishap and incomplete abortion occur in around 2% of cases (Frank, 1985). In the developed world this is a significant statistic. When viewed in the context of the developing world, with limited access to skilled medical care, represents a very important problem.

Around a third of all terminations in the United Kingdom are performed before eight weeks gestation, a similar percentage being performed at this gestation in the United States and a much higher percentage in the rest of Europe (Tietze & Lewit, 1981). Before eight weeks gestation, most spontaneous abortions are complete and surgical evacuation of the uterus is not required. If a suitable agent were used to induce abortion before this gestation, termination of pregnancy should be possible without resort to surgery. Bearing the limitations of surgical termination of pregnancy in mind, and remembering that the earlier the gestation, the safer the abortion, medical termination of early pregnancy is an attractive concept. Suitability of an agent for induction of early abortion does not only depend upon its efficacy and safety, however, but also on its acceptability to women and it is this last requirement that has in the past proved most difficult to fulfil. In this first section of the literature review, induction of early abortion with prostaglandins and the antiprogesterone mifepristone (RU 486) will be discussed.
Myometrial Controls.
In order to consider induction of abortion it is helpful to review various factors which regulate myometrial contractility. Most substances cause their biological effect by binding to a specific receptor. Regulation of myometrial function is mediated by intracellular steroid receptors, which exert a long-term response at a genomic level, and by plasma membrane receptors that cause rapid responses. Substances generated in adjacent tissues, such as decidua or endometrium, can also influence myometrial function.

Information generated by the interaction between a substance and a myometrial plasma membrane receptor is carried into the cell by a transduction system which is made up of the receptor, a transducer and an effector. The effector is usually an enzyme that generates several molecules of a "second messenger" in response to the binding of a ligand (the first messenger) to the receptor. In this way there is amplification of the first messenger's signal and a cellular response is initiated. For a review of myometrial plasma membrane receptor type, structure and effectors, see Fuchs 1995.

The contractile state of myometrial cells is influenced by the intracellular concentration of calcium (Monga & Sanborn, 1995). All excitatory myometrial plasma membrane receptors are coupled to calcium-mobilising effectors. Conversely, inhibitory receptors are coupled to calcium-sequestrating effectors or effectors that inhibit calcium mobilisation (Fuchs, 1995). The myometrial quiescence of pregnancy is associated with a low concentration of intracellular calcium and dephosphorylation of the 20 kilo Dalton light chain subunit of myosin, the primary protein of smooth muscle thick filaments, by myosin light chain phosphatase. Although pregnancy does not increase myosin light chain phosphatase activity, very low levels of myosin light chain phosphorylation are found in human pregnant myometrium (Word et al, 1993) and it is thought that this change, mediated partially by intracellular calcium, aids uterine quiescence (Word, 1995).

Oxytocin is the most specific uterotonic ligand for the myometrium. Although messenger ribonucleic acid (mRNA) for the human oxytocin receptor can be found in non-pregnant breast, ovary and endometrium, it has not been isolated from non-pregnant myometrium. It is found in myometrium at 13 weeks gestation and in greater amounts at term (Kimura et al, 1992). Uterine response to oxytocin depends on oxytocin receptor concentration (Fuchs et al, 1983) with maximal uterine responsiveness to oxytocin coinciding with peak values of oxytocin receptor concentration (Fuchs, 1985).
Myometrial oxytocin receptors mediate increases in intracellular calcium (Schrey et al, 1986) and the contractile response of myometrium to oxytocin is greatly reduced in the absence of extracellular calcium (Coleman, McShane & Parkington, 1988; Batra, 1985).

As mentioned above, the oxytocin receptor is present in other tissues of the reproductive tract with the endometrium and decidua being major target organs for oxytocin. Endometrial oxytocin receptors are linked to the effector phospholipase C (PLC) which generates inositol triphosphate (IP3) as one of its second messengers (Berridge, 1993; Schrey et al, 1986; Mirando et al, 1993) and the cellular response consists of release of prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α).

Oxytocin receptor concentration is under hormonal control. In non-pregnant women there are low concentrations of oxytocin receptor in the myometrium and endometrium, with few cyclical changes and a small nadir midcycle (Fuchs et al, 1985; Fuchs & Behrens, 1993). An increase in oxytocin receptor concentration is seen at the beginning of the second trimester and continues to increase with a peak concentration during delivery. Decidual concentrations are similar or higher than myometrial concentrations and in contrast to other species, progesterone does not appear to have an inhibitory influence on oxytocin receptor expression (Fuchs, 1995).

Human non-pregnant and pregnant myometrium contains all prostanoid receptors and receptor subtypes and binds significantly more PGE2 than PGF2α (Wakeling & Wyngaarden, 1974). Contractile responses are mediated by PGE2, F2α and thromboxane receptor subtypes. These excitatory receptors, in common with the oxytocin receptor, activate the PLC/IP3 transduction system. However, unlike oxytocin receptors, ovarian hormones do not significantly influence the concentration of prostanoid receptors (Fuchs, 1995).

PGE2 and PGF2α can cause long-lasting enhancement of the action of the other contractile agonists such as oxytocin, at concentrations that would not by themselves induce myometrial activity (Coleman & Parkington, 1988). PGF2α releases calcium from a different myometrial intracellular store than oxytocin, so this enhancement of oxytocin activity by PGF2α may be secondary to release of calcium from an usually oxytocin-inaccessible store (Coleman et al, 1988). It may be that this enhancement of other agonists' actions by prostaglandins is of more excitatory consequence than a direct action of prostaglandins on contractile activity.
Ovarian steroids influence myometrial growth and regulate receptor function. Oestrogen is needed for the expression of most uterine receptors having both inhibitory and stimulatory influence on receptor expression. Progesterone exerts a similar influence, down-regulating its own receptor in target cells by inhibiting transcription of the gene encoding the progesterone receptor (Reed et al., 1981; Wei et al., 1988) and down-regulating the oestrogen receptor (Okulicz et al., 1981). Progesterone can also regulate components of signal transduction pathways without affecting receptor concentration. Some progesterone metabolites have been shown to be more potent inhibitors of uterine contractility than the parent molecule (Kubli-Garfias et al., 1979) and multiple mechanisms exist in the uterus for progesterone-mediated inhibition of contractions. Progesterone metabolites have been shown to act as Gamma-aminobutyric acid (GABA) receptor agonists inhibiting myometrial activity in vitro (Putnam et al., 1991).

Progesterone induces the disappearance of myometrial adrenergic, cholinergic and peptidergic innervation during pregnancy, preventing the potent smooth muscle agonistic action of catecholamines (Sjorberg et al., 1984). Sex steroids regulate mast cell activity in the reproductive tract and mast cell mediators, histamine and serotonin, potentiate the uterotonic action of PGF2α in vitro (Rudolph et al., 1993). Nitric oxide has been suggested as a factor influencing uterine quiescence during pregnancy and there is some evidence for the influence of progesterone on the L-arginine-nitric oxide-cGMP system (Garfield et al., 1995).

Another ovarian steroid dependent control of myometrial contractility is the regulation of gap junction formation by oestrogen and progesterone. Gap junctions are specialised regions of the cell membrane at which pores or channels form between neighbouring cells, allowing the exchange of small metabolites and ions (Lowenstein, 1987). In the myometrium, gap junctions provide low resistance pathways between cells, facilitating electric and metabolic coupling and favouring improved contractility (Cole et al., 1985; Miller et al., 1989). Although gap junction plaques are undetectable or present in very low numbers during most of the pregnancy with a corresponding uterine quiescence, the onset of labour is associated with a dramatic increase in the size and number of plaques and a consequent increase in electrical conductivity of the myometrium with co-ordinated contractions (Miller et al., 1989). Change in the ratio of oestrogen to progesterone affects gap junction presence in myometrial cells with oestrogen having a stimulatory and progesterone an inhibitory influence on gap junction numbers (Mackenzie & Garfield, 1985).
The pores of the gap junction channels which connect the interior of the two adjacent cells are made up of proteins called connexins (Beyer et al, 1987). In myometrium connexin-43, a 43 kilo Dalton protein is the major component of the gap junction and has been shown to be influenced by oestradiol and progesterone (Petrocelli & Lye, 1993).

**Early Pregnancy.**

Early human pregnancy is dependent on a continuous secretion of progesterone by the corpus luteum. The corpus luteum is maintained by the secretion of human chorionic gonadotrophin (hCG) by the conceptus (Ross, 1979) until the luteoplacental shift of progesterone synthesis occurs around seven weeks gestation and the placenta becomes the dominant source of progesterone (Csapo, 1969). If luteectomy is performed before the luteoplacental shift is well advanced, abortion will occur as a result of progesterone withdrawal (Csapo et al, 1973a; Csapo et al, 1973b). Progesterone secreted by the corpus luteum primes the endometrium to provide a suitable environment for successful implantation (Findlay, 1983). Csapo has suggested that synthesised progesterone allows maintenance of normal pregnancy by regulating the balance of myometrial suppression (by progesterone) and stimulation (by endogenous prostaglandins), so keeping the uterus in a relatively quiescent state (Csapo, 1977).

The absence of uterine activity in the progesterone "blocked" uterus is, in part, attributable to a dearth of endogenous prostaglandins which are well known to be uterotonic. Progesterone inhibits endometrial prostaglandin production *in vitro* (Abel & Baird, 1980) and, in early intrauterine and ectopic pregnancy, the capacity for decidual prostaglandin synthesis is greatly reduced (Maathius & Kelly, 1978; Abel et al, 1980). The role of progesterone in the inhibition of prostaglandin synthesis and contractility is not fully understood but it has been suggested that progesterone-induced inhibitors may mediate this effect (Abel et al, 1980). That progesterone is known to stimulate decidual synthesis of a large number of pregnancy-specific proteins, adds weight to this theory (Bell, 1985), and as discussed earlier there seem to be multiple mechanisms for progesterone-mediated uterine relaxation.

In addition to inhibiting prostaglandin synthesis, progesterone increases metabolism of prostaglandin both *in vitro* (Kelly et al, 1986) and *in vivo*, with placental progesterone concentrations being closely positively correlated with 15α-hydroxy-prostaglandin dehydrogenase activity (Falkay & Sas, 1978). As the synthetic capacity of the placenta for prostaglandin production increases from around seven weeks
(ie. the time of the luteoplacental shift) onwards, the increased catabolism of prostaglandins which follows increasing placental maturity provides another mechanism for maintenance of uterine quiescence (Kierse, 1985). It is significant that E series prostaglandins, in placental tissue homogenates, with their greater oxytocic potential, are metabolised faster than F prostaglandins (Kierse & Turnbull, 1975).

Although the pregnant uterus is a "suppressed" organ throughout pregnancy, it is most refractory to stimulation while dependent on ovarian steroids for this suppression prior to the luteoplacental shift. Using infusion rates of oxytocin as high as 128 mU/min (Csapo, 1969) and 250 mU/min (Csapo & Pulkkinen 1978) Csapo could obtain no contractile response from the uterus at seven weeks gestation, though after 14 weeks gestation the uterus contracted in response to a similar dose infusion (Bengtsson & Csapo, 1962). This resistance to stimulation by oxytocin which is known to stimulate decidual prostaglandin production (Fuchs et al, 1981), reflects not only the poor prostaglandin synthetic capacity of the decidua in early pregnancy (Maathuis & Kelly, 1978; Abel et al, 1980) but also the low concentration of myometrial and decidual oxytocin receptors which persists until mid-pregnancy (Fuchs et al, 1984), and meant that little progress was made in the development of methods of early medical termination until alternative oxytocic agents became available for use in the form of exogenous prostaglandins.

**Prostaglandins.**

Since the identification and determination of the structure of von Euler's (von Euler, 1935) "prostaglandins" by Bergström and others in the early 1960s (for review see Samuelsson, 1976), there has been extensive investigation of the oxytocic properties of the E and F series of these C20 long-chain hydroxy fatty acids. Bygdeman et al were the first to report the effects of PGE₁ and PGE₂ on the pregnant human uterus in vivo (Bygdeman et al, 1968). They found that, contrary to in vitro observations of inhibition of myometrial motility with increasing doses of PGE₁, intravenous infusion of PGE₁ and PGE₂ stimulated uterine activity in mid and term pregnancy even with a 75-fold increase in dose.

Early studies of the use of E and F series prostaglandins as abortifacients were not designed to look specifically at termination of early pregnancy. In general, these were dose-finding exercises, making no distinction between early first and midtrimester pregnancy. The initial investigations were of abortion induced by continuous intravenous infusions of prostaglandin. Karim and Filshie reported the successful abortion of 14 out of 15 women between 9 and 22 weeks gestation using intravenous
prostaglandin $F_{2\alpha}$ (PGF$_{2\alpha}$). A dose of 50 $\mu$g / minute of PGF$_{2\alpha}$ was infused (12 times greater than that required to stimulate the term uterus) for a range of 4 to 27 hours, until abortion was achieved. Despite pretreatment with parenteral opiate and antiemetic agents, over 20% of women experienced vomiting and 50% diarrhoea (Karim & Filshie, 1970a). Embrey used an intravenous infusion of 2 $\mu$g to 5 $\mu$g / minute of PGE$_2$ or PGE$_1$ to induce abortion in 9 out of 11 women between 9 and 28 weeks of pregnancy. He found that the total dose required to induce abortion with PGE was 5 to 10 times higher than that to induce labour. Two patients vomited during treatment and the incidence of pain or use of analgesia was not reported (Embrey, 1970). In a larger series, Karim & Filshie induced abortion in 50 out of 52 women between 9 and 20 weeks gestation, using PGE$_2$, 11 of these women being in the first trimester. 5 $\mu$g / minute of PGE$_2$ was infused for an average of 14 hours and there was no apparent correlation between gestation and the total dose requirement of PGE$_2$. Twenty five per cent of the women experienced gastrointestinal side effects (vomiting, diarrhoea or nausea) despite premedication with an antiemetic (Karim & Filshie, 1970b). With the aim of reducing induction-abortion intervals, Hillier and Embrey investigated high-dose infusions of PGE$_2$ and F$_{2\alpha}$ resulting in only a 50% abortion rate and what they described as "an intolerable" level of side effects (Hillier & Embrey, 1972).

Although there was some variation in the successful abortion rate in early studies of intravenous prostaglandin, they were consistent in several respects. They showed that PGE$_2$ was a more powerful and also more uterospecific oxytocic than PGF$_{2\alpha}$. Effective doses of PGE$_2$ were 5 to 10 times less than PGF$_{2\alpha}$ and did not appear to cause such a great gastro-intestinal upset, particularly with regard to diarrhoea.

However, PGE$_2$ infusion caused a phlebitic reaction at the infusion site in at least 40% of cases which made prolonged infusion (such as was required to successfully induce abortion) troublesome (Embrey & Hillier, 1971). On balance, the incidence of side effects experienced when effective doses of both PGE$_2$ and PGF$_{2\alpha}$ were infused was felt to be too high and other systemic as well as local methods of prostaglandin administration for induction of abortion were investigated.

Orally administered PGF$_{2\alpha}$ and PGE$_2$ were shown to effectively induce labour at term with low gastro-intestinal or cardiovascular side effects (Karim & Sharma, 1971a). However, the dose of prostaglandin required to induce uterine activity in mid-pregnancy was accompanied by intense gastro-intestinal upset. Karim found in his study of eight women of between 14 and 18 weeks gestation that the threshold dose of PGE$_2$ and F$_{2\alpha}$ for stimulation of the uterus was 2.5 mg and 25 mg
respectively. To induce regular uterine activity, 5 mg of PGE2 and 50 mg PGF2α was required. However, this dose was insufficient to induce abortion in any of the women and, in addition, caused acute watery diarrhoea and vomiting, precluding any further increase to effective doses (Karim, 1971a).

Neither intravenous or oral administration of prostaglandins PGE2 or PGF2α offered any advantage over surgical termination of early pregnancy. Intravaginal administration, however, with its ease of application and potential for local as well as systemic effect, seemed more promising as an agent for early medical termination of pregnancy.

Karim and Sharma vaginally administered ethanol solution of 20 mg PGE2 or 50 mg PGF2α on lactose tablets to 45 women of between 7 and 23 weeks gestation every two and a half hours until abortion. Eight women were in the first trimester. All women aborted with five women requiring curettage after abortion. The induction - abortion interval of 13 hours 15 minutes was comparable to that with intravenous prostaglandin. No mention is made of which women required curettage. Side effects were predominantly gastro-intestinal with 15% of women studied experiencing vomiting or diarrhoea (Karim & Sharma, 1971b). This comparatively low incidence of gastro-intestinal side effects was not confirmed by a review of 1048 cases of a similar gestational range (6 to 20 weeks) and identical dose regime where 64% of women experienced vomiting and 36% diarrhoea, although success rates were comparable (95%) (Southern, 1976).

Karim studied the effect of vaginal PGE2 and PGF2α on 12 women within 2 to 7 days of their missed period and induced complete abortion in 77% of pregnant women (8 out of 9). A maximum of three doses of 20 mg PGE2 or 50 mg PGF2α was given with five women complaining of pain subsequent to administration but few gastro-intestinal side effects (Karim, 1971b). Other authors have confirmed a similar efficacy of 60 to 80% in the early first trimester but report a higher incidence of gastro-intestinal side effects (Bolognese & Corson, 1973; Jones et al, 1974; Tredway & Michell, 1973) suggesting a predominantly systemic action of vaginally administered prostaglandin E2 and F2α.

The rapid metabolism of PGE2 and PGF2α in the circulation means that large doses must be administered systemically to induce adequate uterine contractility for abortion to occur in early pregnancy when the uterus is most resistant to stimulation. Studies of systemic administration of PGE2 and F2α are consistent in their reporting of dose-related side effects, particularly gastro-intestinal side effects.
Prostaglandins, however, unlike oxytocin, can act locally following exogenous administration and the use of intrauterine PGE$_2$ and F$_{2\alpha}$ was studied extensively as a means of early medical termination of pregnancy.

Wiqvist and Bygdeman obtained a 92% abortion rate when up to 1050 $\mu$g PGE$_2$ and 5400 $\mu$g PGF$_{2\alpha}$ were injected into the extra-amniotic space of 13 women of between five and 13 weeks gestation (Wiqvist & Bygdeman, 1970b). This method of administration of prostaglandin was as effective as intravenous administration (Wiqvist & Bygdeman, 1970a) but with significantly fewer side effects - correlating with smaller doses of prostaglandin.

Embrey and Hillier induced abortion in 14 of 15 women between 6 and 20 weeks gestation (three less than 8 weeks, one at 10 weeks) using one to two hourly injections of PGE$_2$ or F$_{2\alpha}$ into the extra-amniotic space, a mean of 1,177 $\mu$g PGE$_2$ and 3650 $\mu$g PGF$_{2\alpha}$ being given in total over a mean period of 18 hours. All the first trimester pregnancies were aborted completely with three midtrimester abortions being incomplete. Twelve women experienced vomiting (80%) and no comment is made regarding pain (Embrey & Hillier, 1971).

Wiqvist et al induced abortion in 65 of 70 women in the first and second trimester using intermittent extra-amniotic injections of PGF$_{2\alpha}$ titrated against the patient's pain. Eight women of 7 to 8 weeks gestation aborted as did 12 women of less than 12 weeks with 45 of the 50 midtrimester patients aborting. It does not state in the study if the early first trimester abortions were complete. Overall the dose of PGF$_{2\alpha}$ used was 10 to 20 times less than that required by the intravenous route. Notably the dose of prostaglandin required in the 7 to 8 week group was half that of the 9 to 12 week group and the induction - abortion interval only 6.2 hours - a quarter of that in the midtrimester group. The incidence of gastro-intestinal side effects was low but 20% of women experienced severe pain and 5% of the women developed pelvic infection requiring antibiotic treatment (Wiqvist et al, 1972).

In an extension of their earlier study (Embrey & Hillier, 1971) Embrey et al induced abortion in 82 of 94 women in the first and second trimester using extra-amniotic PGE$_2$ and F$_{2\alpha}$. Ten of the 11 first trimester patients abortion. However, unlike Wiqvist et al (1972), the induction - abortion interval was not significantly shorter. The majority of women required surgical evacuation of the uterus, 27% experienced vomiting and 5% diarrhoea. Four women exhibited a marked reaction to prostaglandin injection attributed to inadvertent intravenous administration of prostaglandin (Embrey et al, 1972).
Both of these studies (Embrey et al, 1972; Wiqvist et al, 1972) concluded that extra-amniotic administration of prostaglandins for the induction of early abortion conferred no advantage over surgical evacuation of the uterus, a fact underlined by Roberts et al in their small study of extra-amniotic PGE2 in the first trimester resulting in only a 65% success rate and 20% infection rate (Roberts et al, 1971).

Csapo studied the efficacy of what he called "prostaglandin impact" for early termination of pregnancy - in effect a large extra-amniotic bolus of prostaglandin rather than repeated small injections. He hypothesised that by compromising the conceptus with a massive initial dose of prostaglandin (through uterine vasoconstriction and contractions), support of the corpus luteum is decreased and the consequent luteolysis leads to progesterone withdrawal. This, in turn, renders the previously suppressed uterus contractile by the release of endogenous prostaglandin and, as in surgically lute-ectomised patients, further exogenous prostaglandin is not required to induce abortion (Csapo et al, 1973c). The concept of secondary medical lute-ectomy was explored to a lesser degree by Karim (Karim, 1971b). Clinical studies using initially 10 mg then 5 mg PGF2α or 1 mg PGE2 injected over 10 minutes into the extra-amniotic space in the early first trimester, yielded high complete abortion rates which were comparable with surgical termination (Csapo et al, 1972; Csapo et al, 1973c; Moscary & Csapo, 1973). However, despite the stated aim that prostaglandin impact should "resemble a normal menstrual period, rather than an abortion" (Csapo et al, 1973c) the procedure was not tolerable without premedication with intravenous opiate and benzodiazepine in addition to rectal antiemetic. Even with the administration of these drugs prior to treatment, there was still a 25% incidence of vomiting. In addition, as found by Embrey et al (1972), there was the risk of inadvertent intravenous dosage. In one study the incidence of side effects attributable to this was 18% (Csapo et al, 1973c).

Although other studies have confirmed Csapo’s success rate (Ragab & Edelman, 1976; Karim, 1973) by combining the results of Lichtman and Jones (Lichtman et al, 1974; Jones et al, 1975) an overall success rate of only 70% is obtained (see also Roberts et al, 1971) with a 44% incidence of infection. In one large comparative study of intrauterine PGF2α and vacuum aspiration (without general anaesthesia) in early pregnancy, prostaglandin use was associated with a 30% incidence of vomiting and diarrhoea (versus 9% in the vacuum aspiration group) (Ragab & Edelman, 1976).
In summary, the naturally occurring prostaglandins E\textsubscript{2} and F\textsubscript{2α} do not lend themselves to use as agents for the induction of early abortion. Side effects subsequent to the high doses needed to complete abortion when they are used systemically, render this method of delivery impractical. Technical difficulties in addition to an increased risk of infection, prostaglandin related collapse and side effects, preclude their use locally as a means of medical termination of early pregnancy.

**Prostaglandin Analogues.**

The rapid inactivation of prostaglandin E\textsubscript{2} and F\textsubscript{2α} in the circulation was identified as a clinical disadvantagement during studies of their use systemically as abortifacients. The high doses required to induce abortion were accompanied by a high incidence of side effects. In 1971, however, Bundy et al published details of 15-methyl analogues of PGE\textsubscript{2} and F\textsubscript{2α}. They found that by altering the configuration of the natural molecule by the additional of an alkyl group at C\textsubscript{15}, it was no longer a substrate for enzymatic degradation by 15-hydroxy prostaglandin dehydrogenase but retained smooth muscle stimulating properties in *in vitro* experiments (Bundy et al, 1971). Animal studies revealed a potential clinical superiority of these analogues over the parent compounds with a demonstration of enhanced potency and duration of activity compared with PGE\textsubscript{2} and F\textsubscript{2α} when the 15-methyl analogues were administered to pregnant rhesus monkeys (Kirton & Forbes, 1972). The potential advantage of such compounds for medical abortion was large. Clinical interest increased further with the discovery that the introduction of a methyl group at C\textsubscript{16} rendered analogues more resistant to oxidation of the 15-hydroxy group (Yankee & Bundy, 1972) and the subsequent development of the "third generation" analogues. Many compounds were developed but subsequently abandoned because of insufficient activity, lack of stability or adverse reactions. For the purposes of this literature review I will concentrate on those analogues which have sustained clinical interest.

Bygdeman et al conducted the first clinical study with 15-methyl PGF\textsubscript{2α} demonstrating that intrauterine administration of the analogue in early pregnancy was an effective abortifacient (Bygdeman et al, 1972). However, as discussed before, invasive methods of medical termination of early pregnancy are of no benefit, requiring skilled personnel for their use and having the disadvantage of increased rates of infection and side effects when compared with vacuum aspiration (Lichtman et al, 1974; Jones et al, 1975; Roberts et al, 1971; Ragab & Edelman, 1976). In a study of the effects of intravenous or intramuscular delivery of 15-methyl PGF\textsubscript{2α} on the mid pregnant uterus, Toppozada et al showed that the analogue had 10 times the uterotonic potency of the parent compound in
addition to a two-fold increase in duration of biological activity. They found that, unlike intramuscular injection of natural prostaglandins, 15-methyl-PGF$_{2\alpha}$ did not cause local inflammation at the injection site and, therefore, had potential for non-invasive delivery (Toppozada et al, 1972).

Intramuscular 15-methyl PGF$_{2\alpha}$ was found to be an efficient abortifacient in both early and midtrimester pregnancy with around 90% of women less than 8 weeks gestation aborting completely (Fylling & Jerve, 1977). However, the majority of women suffered vomiting, diarrhoea and pain (in one large study a mean of three episodes of vomiting and diarrhoea each woman) (WHO, 1977a) and the usefulness of intramuscular 15-methyl PGF$_{2\alpha}$ as an abortifacient was questioned (Laurensen & Wilson, 1975; Fylling & Jerve, 1977; Karim & Sharma, 1972; WHO, 1977a; Bygdeman & Christensen, 1983). The discovery that the methyl ester of 15-methyl PGF$_{2\alpha}$ was ten times more potent than the free acid (Karim & Sharma, 1972) and also stable in suppository fat, offered hope that vaginal administration of F analogue prostaglandin could provide an acceptable form of early medical abortion.

It was suggested that if a suitable base was used for vaginal suppositories containing prostaglandin analogue, the high peaks of plasma concentration found following intramuscular injection could be avoided leading to a significant reduction in side effects (Bergström et al, 1976). This mode of delivery of prostaglandin would also offer the potential for unskilled, even self-administration.

Three hourly administration of 1 to 1.5 mg 15-methyl PGF$_{2\alpha}$ methyl ester pessaries induced complete abortion in 97% of 50 women less than 7 weeks gestation in a study by Bygdeman et al (Bygdeman et al, 1976a,b). In a comparative study of the methyl ester in vaginal suppository form and 15-methyl PGF$_{2\alpha}$ free acid given intramuscularly, vaginal delivery was found not only to be more effective, with a 100% abortion rate, but also to cause fewer prostaglandin-related side effects (Fylling & Jerve, 1977). Although vaginal suppositories of 15-methyl PGF$_{2\alpha}$ methyl ester caused fewer side effects than intramuscular injection of the free acid, significant numbers of women continued to experience vomiting and diarrhoea in addition to pain. This problem was addressed by the investigation of methods of slow vaginal delivery of the F analogue. Bygdeman et al compared vaginal delivery of up to 10 mg of 15-methyl-PGF$_{2\alpha}$ methyl ester via a silicon slow release device with three hourly administration of 1 to 1.5 mg in adeps solidus base pessaries. Despite premedication with oral opiate and antiemetic there was no difference between the two groups in terms of side effects or efficacy. Over 50% of women required
additional parenteral opiate analgesia and experienced both vomiting and diarrhoea. Complete abortion rates in both groups of women (all less than 7 weeks gestation) approached 100%. No real clinical benefit of the slow release device was discerned save for the avoidance of repeated vaginal administration (Bygdeman et al, 1976c).

Mandelin studied the effect of a single 3 mg 15-methyl PGF$_{2\alpha}$ methyl ester long acting pessary (witepsol E-76 base) on 104 early pregnancies. Despite analgesia and antiemetic premedication 87% of women experienced moderate to severe pain and 6% either vomiting or diarrhoea. In addition, the complete abortion rate was only 76% (Mandelin, 1978); indeed, more than 20% lower than that of Bygdeman et al (Bygdeman et al, 1976c). This comparative inefficiency was confirmed by Csapo and Pulkkinen who used the same pessary to obtain a 70% complete abortion rate, though admittedly in slightly later first trimester pregnancy (10.9 ± 0.5 weeks gestation) (Csapo & Pulkkinen, 1979).

In the late 1970s three stable E series analogues became available for clinical investigation:

16-phenoxy-o-17,18,19,20-tetranor PGE$_2$ methyl sulfonylamide (sulprostone, Schering) given as an intramuscular injection;
9-deoxo-16,16-dimethyl-9-methylene PGE$_2$ (meteneprost, Upjohn) stable in suppository fat therefore suitable for vaginal administration;
16,16-dimethyl-trans-A$^2$-PGE$_1$ methyl ester (gemeprost, May & Baker) also stable as a vaginal pessary (Figure 1.1).

Earlier studies with another E analogue, 16,16-dimethyl PGE$_2$ (subsequently abandoned because of its instability in suppository fat for long-term storage) demonstrated the potential advantages of analogues of the prostaglandin E series. Complete abortion rates were in general higher than with F series analogues and as good as vacuum aspiration at the same gestation, consistently around 90%. In addition, gastrointestinal side effects appeared to be less frequent using the E analogue (Lundström et al, 1977; Mackenzie et al, 1978; Rosen et al, 1979).

Studies with the stable E analogues investigated the role of prostaglandins as abortifacients in a more defined way than earlier studies with natural prostaglandins E$_2$ and F$_{2\alpha}$ and the 15-methyl analogues. Prostaglandins and their analogues had been shown to have an undisputed role in the induction of midtrimester abortion. However, previous studies did not provide a convincing argument for their use as an alternative to first trimester surgical techniques. In the majority of studies with stable E series analogues much closer heed was paid to acceptability of the method, by
detailed documentation of side effects. In addition, it was realised that the incidence of complete abortion was higher when treatment with prostaglandin was limited to the first seven or eight weeks of pregnancy. This observation had long been made anecdotally of spontaneous abortion occurring prior to the luteoplacental shift, when curettage is rarely required to complete evacuation of the uterus (Bygdeman, 1984). Almost all studies of stable E analogues as abortifacients in the first trimester were, therefore, restricted to the first eight weeks gestation.

Karim et al (1977) and Takagi et al (1978) conducted early dose finding studies with gemeprost which suggested that a 1 mg pessary given vaginally every three hours to a maximum of five pessaries represented the most effective regime for induction of early abortion with almost 90% of women treated aborting completely. Although Takagi's abortion rate was matched in subsequent studies using the same dose regime (Smith & Baird, 1980; WHO, 1982a), the low incidence of side effects could not be repeated. Smith and Baird studied 90 women of less than 49 days amenorrhoea, randomising them to treatment with gemeprost or vacuum aspiration under local or general anaesthesia. Although they found prostaglandin treatment as efficacious as vacuum aspiration under local anaesthetic (both groups had 87% complete abortion rate) 42% of women experienced moderate to severe pain, 42% of women vomited and 33% experienced diarrhoea during administration of gemeprost (Smith & Baird, 1980). A larger multicentre study of 358 women of less than 56 days amenorrhoea receiving the same dose of gemeprost yielded an almost identical complete abortion rate (86%) and a similarly high incidence of gastrointestinal side effects and pain (24% vomiting, 27% diarrhoea and 29% pain) (WHO, 1982a). The reason for this discrepancy in side effects recorded, probably lies with the fact that women in Takagi's trial were allowed to self administer all pessaries, subsequent to the first, at home, while in these other trials pessaries were given by staff members in hospital. A similar difference, particularly in the incidence of pain, has been noted in studies comparing home and hospital based prostaglandin termination of early pregnancy (Bygdeman et al, 1983; Rosen et al, 1984). Studies of controlled release of gemeprost were as disappointing as those conducted with 15-methyl-PGF2α methyl ester. Cameron and Baird obtained an 85% complete abortion rate using 3 mg of gemeprost administered vaginally via a polyethylene-oxide based hydrogel over 24 hours. Although the dose of gemeprost was minimised (median dose received over 24 hours was only 1.65 mg) 84% of women experienced moderate to severe pain with 38% suffering either vomiting or diarrhoea (Cameron & Baird, 1986). Bygdeman et al were similarly unsuccessful in limiting prostaglandin related side effects when administering gemeprost in a different slow release device made of a 3-layered water soluble polymer (Bygdeman et al, 1984).
Prostaglandin E series analogues

PGE₁

PGE₂

Sulprostone

Meteneprost

Gemeprost

Figure 1.1
Meteneprost, like gemeprost, is stable in suppository fat and suitable therefore for vaginal administration. Bygdeman et al, in a series of studies, demonstrated its efficacy as an early abortifacient at home or in hospital, and in comparison with both vacuum aspiration and other stable E analogues (Bygdeman et al, 1980a; Bygdeman et al, 1981; Bygdeman et al, 1983; Rosen et al, 1984). In these studies of women with less than 50 days amenorrhoea, the complete abortion rate was between 92 and 100% using a variety of dose regimes (chronologically: 75 mg twice 6 hourly; 75 mg followed by 30 mg 6 hours later; 60 mg followed by 45 mg 6 hours later; 50 to 60 mg twice 6 hourly). Although the requirement for intramuscular opiate was greatly reduced by self-administration of pessaries at home (3 to 6% versus 32 to 39% of women in hospital), the incidence of vomiting and diarrhoea was constant, affecting around 50% of women and meteneprost was found to cause a more marked hyperpyrexia than either gemeprost or sulprostone.

Sulprostone is also an E2 analogue. It is given by intramuscular injection with 0.5 mg 3-hourly to a maximum of three injections seeming to be the optimal regime (Bygdeman et al, 1980a). It compares well in terms of efficacy with vacuum aspiration, with complete abortion rates of between 91% in a large multicentre trial (WHO, 1987) to 94% in smaller studies (Bygdeman et al, 1983). Its intramuscular administration precludes self-treatment and probably accounts for the higher incidence of severe pain when sulprostone rather than vaginally administered E analogues are used. Bygdeman et al found that 56% of 34 women given sulprostone required intramuscular analgesia compared with 32% of 63 women receiving gemeprost and 34% of 56 women receiving meteneprost, despite premedication with oral analgesia in all women (Bygdeman et al, 1983). The situation is analogous to that with intramuscular 15-methyl-PGF2α free acid and its vaginally administered methyl ester, with peaks in plasma concentration of analogue exacerbating side effects (Bergström et al, 1976). Gastrointestinal side effects occur in around 50% of women treated with sulprostone (Bygdeman et al, 1980a; Bygdeman et al, 1983).

Rosen et al have shown that the majority of women in their study groups preferred the concept of medical termination of early pregnancy when compared with surgical termination of early pregnancy and despite a formidable high incidence of prostaglandin related side effects, women subsequently treated with prostaglandins remained loyal to medical termination of pregnancy (Rosen et al, 1979; Rosen et al, 1984). Hill and Mackenzie in a retrospective study of prostaglandin induced medical abortion, compared with vacuum aspiration, state that over 75% of women found treatment acceptable despite the use of methods and
prostaglandins known to cause objectively unacceptably high levels of side effects such as intrauterine prostaglandin E₂ and vaginal 15-methyl PGF₂₅α methyl ester (Hill & Mackenzie, 1990). The stable and relatively uterospecific E series analogues, though preferable to prostaglandins E₂, F₂α and F analogues, are known to cause more pain than surgical methods of abortion, induce vomiting and diarrhoea in half the women treated, in addition to resulting in a longer period of bleeding than that following vacuum aspiration. For women to repeatedly claim as acceptable a method of abortion which to the objective eye is anything but, illustrates the need women have for an alternative to surgical termination of pregnancy.

In summary, prostaglandin analogues present certain clinical advantages over naturally occurring prostaglandins in their use as early abortifacients. They are significantly more potent and stable than prostaglandins E₂ and F₂α, allowing effective non-invasive administration. However, although they successfully induce complete abortion in early pregnancy, the high incidence of side effects such as pain, vomiting and diarrhoea limits their usefulness as agents for medical termination of early pregnancy.

**Antiprogesterones.**

As discussed earlier in this review, progesterone is essential for the establishment and maintenance of human pregnancy. In 1937, Robert Courrier described its importance thus:

"Progesterone is the hormone of the mother - it is indispensable for reproduction".

(Courrier, 1937).

In the 1970s Csapo elegantly demonstrated this indispensability in a series of clinical experiments. He showed that lute-ectomy performed prior to an advanced luteoplacental shift (around 50 days amenorrhoea) resulted in abortion in 7 out of 11 women. The four women who failed to abort, unlike the seven aborters, did not have a sustained fall in progesterone levels beyond the first 24 hours following lute-ectomy. Maintenance of progesterone levels after lute-ectomy by exogenous progesterone (200 mg intramuscularly daily for seven days) prevented abortion in all seven women treated this way (Csapo et al, 1973a). Exogenous oestradiol administration did not prevent the previously observed effects of lute-ectomy induced ovarian steroid withdrawal, demonstrating the indispensability of progesterone in early pregnancy (Csapo et al, 1973b).
A medical method of progesterone withdrawal has long been sought because, apart from its other effects on reproductive physiology in women, based on Csapo's experience with surgical progesterone withdrawal, such an agent would have huge potential as an abortifacient in early pregnancy.

Pharmacological progesterone withdrawal can theoretically be achieved in three ways - (a) by immunisation with a specific antibody against progesterone, so neutralising circulating progesterone; (b) by inhibiting the synthesis of progesterone; (c) by antagonism of the action of progesterone at the target organ.

The use of progesterone monoclonal antibodies to prevent implantation in a variety of lower mammals such as the mouse (Wright et al, 1982), ferret (Rider & Heap 1986) and rat (Phillips et al, 1988) has been described. This method of progesterone withdrawal has not been examined in women.

Prevention of the conversion of pregnenolone to progesterone can be achieved by inhibiting ovarian 3β-hydroxysteroid dehydrogenase (3β-HSD) activity with several synthetic progestins. However, because these compounds are themselves progestagenic, their clinical use as progesterone "withdrawers" is of no benefit (Shinada et al, 1978). Sterling-Winthrop have developed a group of compounds which competitively inhibit 3β hydroxysteroid dehydrogenase and possess no hormonal agonistic activity. They specifically inhibit the conversion of pregnenolone to progesterone and dehydroepiandrosterone to androstenedione although the inhibitory potential for ovarian / placental steroidogenesis and adrenal steroidogenesis varies between the compounds. Of the compounds developed, Azastene, trilostene and epostane have been found to have the greatest clinical potential by merit of the reversibility of their enzyme inhibition. Trilostane preferentially suppresses adrenal steroidogenesis in the human (van der Spuy, 1983). Azastene preferentially inhibits ovarian / placental steroidogenesis in primates (Schane et al, 1978). Epostane has proven to be the most clinically useful of these compounds as an abortifacient. Administered orally, a dose related fall in progesterone levels occurs with its nadir at four hours and a return to almost pretreatment levels of progesterone by 24 hours. Significant reduction in progesterone levels can be achieved with doses of Epostane which have no effect on adrenal steroidogenesis and the efficacy of progesterone withdrawal increases with increasing gestation, suggesting a preferential inhibition of placental rather than ovarian steroidogenesis (Pattison et al, 1984).
As could be predicted, Epostane is an effective abortifacient in early pregnancy. The reversible nature of its 3βHSD inhibition means that a multiple dose regime is required and although abortion rates following a five day course are reasonably high (Birgersson et al, 1986) a seven day course yields higher abortion rates. Birgersson et al investigated 56 women of less than 49 days gestation given a seven day course of Epostane 200 mg 6 hourly. Overall there was an 84% complete abortion rate. However, five women failed to complete the course of tablets and if the outcome of the remaining 51 women is analysed, an abortion rate of 90% is reached. Nausea and vomiting occurring in 70% were the predominant side effects and the reason for the non-completion of the treatment course in five women. Although day 7 cortisol levels were higher than those on day 0 or 14, all single values remained in normal limits. Of note, the "non-responders" had significantly higher pretreatment progesterone levels (Birgersson et al, 1987).

Using an identical treatment regime, Crooij et al induced complete abortion in 40 (80%) of 50 women less than 56 days amenorrhoea. Eight women did not respond to Epostane and were found to have a smaller fall in progesterone. Eighty six per cent of women experienced nausea and/or vomiting. However, 64% had these symptoms prior to treatment (Crooij et al, 1988). In both these studies, although the majority of women reported pelvic pain, the use of analgesia was very low.

Epostane has been shown to sensitize the uterus to both endogenous (Webster et al, 1985a) and exogenous prostaglandins (Webster et al, 1985b). As a 7-day course of tablets lends itself to non-compliance (and this may explain the lack of response in some women), one method of shortening treatment would be the addition of a potent prostaglandin analogue to treatment with Epostane. Although Epostane has shown great promise as an agent for induction of early abortion, its development has been curtailed by pharmaceutical politics and factors described by Mastroianni in 1990 (Mastroianni et al, 1990).

Antagonism of the action of progesterone at the level of the target organ can be achieved by progesterone receptor blockade. Early compounds found to possess anti-progestagenic properties include gestrinone, anordin and ORF 9371. The former two compounds were found to have some contraceptive activity in both lower mammals (Gu and Chang, 1979) and woman (Sakiz et al, 1974), but in the case of gestrinone this was weak in the luteal phase. In addition, hCG prevented a decrease in ovarian steroid levels following administration of gestrinone even in large doses (Mora et al, 1975) precluding its use as an abortifacient.
Androgenic side-effects and low efficacy in clinical trials limited the usefulness of these compounds as antiprogesterones in clinical practice (Healy, 1985).

In the early 1980s, Teutsch and colleagues at Roussel UCLAF in Paris discovered that bulky dimethylaminophenyl substitution in the 11β position of a 19-norsteroid (norethisterone) conferred antagonistic properties to the compound and that, in addition, hydrophobic 17α-substitution increased the relative binding affinity for the progesterone receptor (Teutsch, 1985). Following the discovery of this antiprogesterone, RU 486 (mifepristone), hundreds of compounds have been synthesised by a variety of pharmaceutical companies and private organisations ZK 98734 (lilopristone) and ZK 98299 (onapristone) synthesised by Schering AG have been extensively investigated in lower mammals (such as the guinea pig, which possesses a luteo-lacental shift of steroid synthesis and in this way resembles the human female) and are the only antiprogestins apart from mifepristone to have undergone clinical testing. Preclinical data suggest a slightly different biological profile of activity (and, in the case of onapristone, mode of action) when compared with mifepristone (Chawlisz, 1994). Clinical data are limited but do not suggest any marked differences in abortifacient potential (for review see Van Look & Von Hertzen, 1993). For the purposes of this review I will concentrate on data reporting the use of mifepristone in the human female but will allude to other species and other antiprogestins where relevant (Figure 1.2).

Mifepristone (RU 486), in addition to being a strong antiprogesterone, is a powerful antiglucocorticoid. This can be explained by the 50% aminoacid sequence homology of the C-terminal, steroid binding region of the progesterone and glucocorticoid receptors (Mishrahi et al, 1987). Mifepristone has antiandrogenic activity which is 20 to 30-fold less than its antiprostational and antiglucocorticoid activity (Philibert et al, 1985) but unlike lilopristone (ZK 98734) it lacks any mineralocorticoid activity. (Henderson, 1987).

Mifepristone has been shown to bind to the progesterone receptor of a variety of different species including human (for review see Van Look & Bygdeman, 1989). In the chicken, where progesterone serves a different role from its mammalian one, mifepristone binds to the glucocorticoid receptor but not to the oviductal progesterone receptor (Groyer et al, 1985). Mifepristone does not bind to the hamster progesterone receptor either (Okulicz, 1987) which in common with the chicken progesterone receptor has a cysteine at position 575 in the steroid binding domain. All receptors that bind mifepristone have a glycine at this position and Benhamou and colleagues have shown that substitution of the cysteine with a glycine at position 575 of the
chicken progesterone receptor allows binding of mifepristone demonstrating that a single amino acid determines the sensitivity of progesterone receptors to RU 486 (Benhamou et al, 1992). It is of note that positioning of the aromatic 11β substitution of these compounds in this hormone binding domain of the progesterone receptors, determines whether the activity generated is agonistic or antagonistic (Benhamou et al, 1992).

![Image of hormone binding structures]

**Figure 1.2**
In vitro studies of the relative binding affinity of mifepristone for the progesterone and glucocorticoid receptor show an increased affinity for the progesterone receptor when compared with progesterone, after prolonged incubation and an increased affinity for the glucocorticoid receptor when compared with dexamethasone (for review see Van Look & Bygdeman, 1989). In vivo biological activity does not, however, necessarily mirror in vitro studies of relative binding affinity (Henderson, 1987).

Following oral administration of mifepristone, peak plasma concentrations are found between one to two hours later (Swahn et al, 1986). It has a high absorption rate after oral administration (70%) with around 40% bioavailability (Deraedt et al, 1985) and its elimination half life is about 20 hours (Swahn et al, 1986). It is distributed more slowly following intramuscular or subcutaneous injection (Deraedt et al, 1985) and its antiglucocorticoid effect is diminished by this route of administration (Henderson, 1987).

Once absorbed, mifepristone is bound to a high-affinity, limited-capacity, plasma binding protein: orosomucoid, an α1- acid glycoprotein, which is saturated at concentrations of mifepristone exceeding 2.5 μM. Mifepristone exceeding the binding capacity of orosomucoid is available for metabolism and liberation into tissues (Heikinheimo et al, 1987a). These findings explain the lack of cumulative effect on serum levels following repeated oral administration observed by Swahn et al (1986) and support Lahteenmäki et al’s suggestion that RU 486 detected in the serum 10 days following a single oral 200 mg dose, represents tissue accumulation of the drug (Lahteenmäki et al, 1987). Carriage of mifepristone by orosomucoid also explains the low (40%) bioavailability of mifepristone following oral administration, which results from significant presystemic first-pass metabolism of available, unbound compound (Van Look and Bygdeman, 1989). As would be expected, there is no direct relationship between circulating levels of mifepristone and the dose administered orally (Swahn et al, 1986; Heikinheimo et al, 1986).

No other animal species have such a plasma binding protein for mifepristone and this could account for differing pharmacokinetic observations between human and other mammalian species (Daraedt et al, 1985). Onapristone is not bound to orosomucoid and as a result has a much shorter elimination half life of 2 to 4 hours compared with 20 hours for mifepristone (Chwalisz, 1994).

Mifepristone is metabolised in the rat by 2 step demethylation of the dimethylaminophenyl side chain at C-11 and by hydroxylation of the 17-propynyl side chain (Deraedt, 1985). Identification of monodemethylated, didemethylated and
hydroxylated metabolites following oral ingestion of mifepristone in the human, suggests a similar metabolism (Baulieu, 1985; Heikinheimo et al, 1987b). Plasma levels of metabolites are dose-dependent, unlike plasma levels of mifepristone, and are present in concentrations that equal or exceed those of mifepristone (Lahteenmäki et al, 1987; Heikinheimo et al, 1987a). These metabolites have significant affinities for both the progesterone receptor (21%, compared with mifepristone) and the glucocorticoid receptor (45 to 61%, compared with mifepristone) and it is probable that they contribute to the antiprostational and antiglucocorticoid effect of mifepristone (Heikinheimo et al, 1987b; Heikinheimo et al, 1987a). Over 90% of mifepristone and its metabolites is excreted in faeces via the biliary system (Deraedt et al, 1985).

To understand the mechanism of action of mifepristone and other antigestagens at a receptor level, it is necessary to review the structure and function of steroid receptors, in particular the human progesterone receptor, complementary DNA for which has been cloned by Misrahi et al (Misrahi et al, 1987). Members of this steroid receptor family share three homologous regions. The first and most highly conserved (C1) encodes the DNA binding domain and the other two homologous regions (C2 and C3) are small segments of the carboxyl terminus which lie within a region important for ligand binding and receptor dimerisation (Evans, 1988).

In the absence of progesterone, the receptor is complexed with several non-steroidal binding proteins. These include two heat shock proteins (HSP), HSP 90, a 90 kiloDalton protein and HSP 70, a 70 kiloDalton protein (Smith et al, 1990). Although in in vitro studies the unliganded progesterone receptor complex is found in the cytosolic fraction of cell homogenates, in vivo, it is nuclear in situation (Perrot-Applanat et al, 1992). In the unoccupied state the receptor complex is oligomeric, basally phosphorylated and unable to bind to DNA. Once progesterone has bound to the receptor, hyperphosphorylation occurs and there is dissociation of the binding protein with the exception of HSP 70. There follows dimerisation of the receptor forms and binding of the resultant receptor dimer to the progesterone response elements of DNA, specific transcription enhancer sites (for review see Horwitz, 1992). There are several possible steps of this sequence with which mifepristone may interfere.

Mullick and Katzenellenbogen demonstrated a heavier sedimentation constant of some RU 486-bound receptor complexes when compared with agonist-progesterone receptor complexes on a sucrose density gradient (Mullick & Katzenellenbogen, 1986). This heavier 65 species is probably due to persistent association of the
receptor with other proteins (El-Ashry et al, 1989). However, Baulieu's suggestion that this retention of heat shock proteins renders the RU 486-progesterone receptor complex inactive and unable to bind to the DNA progesterone response element (Baulieu, 1988) is not borne out in vivo or in vitro.

Baulieu's model does not allow for agonistic properties of mifepristone and it is known to possess both progestational (Gravanis et al, 1985; Koering et al, 1985) and glucocorticoid (Laue et al, 1988) activities. This in vivo evidence of binding of the RU 486-progesterone receptor complex to nuclear DNA is supported by in vitro findings. Mifepristone does not appear to interfere with activation of the progesterone receptor (Horowitz, 1985) or with the high affinity of the progesterone receptor for DNA (Rauch et al, 1985), with RU 486-bound progesterone receptors binding to specific DNA sites with the same affinity as native progesterone-progesterone receptor complexes (El-Ashry et al, 1989).

The RU 486-bound progesterone receptor complex with the progesterone response element of DNA differs from agonist-bound progesterone receptor complex (El Ashry et al, 1989) and the RU 486-bound progesterone receptor can block transcription activation by agonist-bound receptor (Guiochon-Mantel et al, 1988). In addition RU 486 and agonists have different mechanisms of binding to the progesterone receptor (Skafar et al, 1991). It may be these differences which help to interfere with or modify transcription activation of progesterone regulated genes. An alternative mechanism of antagonist action of mifepristone is by a sustained DNA occupancy by the RU 486 progesterone receptor complex associated with a failure of down regulation of the progesterone receptor, which would be seen with an agonist. This model allows for an agonistic action of mifepristone under certain circumstances (for review see Horwitz, 1992).

Mifepristone, lilopristone and onapristone have a similar 2-dimensional structure (see Figure 1.2). However, there are marked 3-dimensional differences between onapristone and the former two antagonists. Onapristone is a 13α-configurated (retro) steroid, whereas mifepristone and lilopristone are 13β-configurated steroids (Neef et al, 1984). As well as this stereochemical difference, the molecular mechanism of action differs: while 13β configurated antagonists promote binding of the antagonist-bound progesterone receptor to the progesterone response element of DNA, onapristone does not. In competitive assays onapristone blocks the DNA binding of RU 486 progesterone receptor complexes and also antagonises agonist activity (Klein-Hitpass et al, 1991). It is, therefore, postulated that there are two types of receptor blocking antiprogestins. There are those that promote binding
of the occupied progesterone receptor to DNA, have agonistic potential and impede transcription. And, there are those (like onapristone) which are "pure" antagonists, blocking the binding of the antagonist-bound progesterone receptor to DNA, possibly by a failure to promote formation of stable receptor dimers (Klein-Hitpass et al, 1991).

Progesterone down regulates its own receptor in target cells by inhibiting the gene encoding the progesterone receptor (Reed et al, 1988; Wei et al, 1988) and also down regulates the oestrogen receptor (Okulicz et al, 1981). As would be expected of a progesterone antagonist, mifepristone influences oestrogen and progesterone receptor concentration. Mifepristone has been shown to increase oestrogen receptor concentration in the myometrium and decidua of pregnant (Haluska et al, 1990) and endometrium of non-pregnant ovariectomised (Neulen et al, 1990) non-human primates. Mäentausta et al demonstrated blockade of progesterone down regulation of oestrogen and progesterone receptor expression by mifepristone administered to non-pregnant women in the early luteal phase (Mäentausta et al, 1993). Shi et al found an increase in nuclear binding sites for oestrogen in the decidua of women given a single dose of mifepristone in the early first trimester (Shi et al, 1992) and in a further study differential distribution of progesterone receptors in the decidua with increase staining for progesterone and oestrogen receptors in the vessels and stromal cells of the decidua parietalis (Shi et al, 1993) suggesting that this may be the primary target site of the antigestagen in the decidua. Mifepristone seems to have a regulatory influence on steroid receptor numbers and distribution in addition to its impact on progesterone receptor binding.

Mifepristone has been shown to have oestrogenic activity in MCF-7 human breast cancer cells where it is thought to bind directly to the oestrogen receptor (Jeng et al, 1993) and it exhibits an oestrogenic action in vivo in rat myometrium which is inhibited by an antioestrogen (Dibbs et al, 1995). Mifepristone has been shown to have a non-receptor mediated, non-competitive, antioestrogenic effect on non-human primate endometrium (Wolf et al, 1989). Unlike progesterone's antioestrogenic effect on endometrium, which is associated with down regulation of the oestrogen receptor (Oculicz et al, 1981) and an increased local metabolism of oestradiol by the progesterone induced increase in 17β hydroxysteroid dehydrogenase in the endometrial epithelium (Tseng & Gurpide, 1975), mifepristone's antioestrogenism is seen in conjunction with an increased number of oestrogen receptors (Neulen et al, 1990) and a blocked expression of 17β hydroxysteroid dehydrogenase (Mäentausta et al, 1993).
Mifepristone acts locally on the target cells of the endometrium and decidua. Bleeding can be induced by mifepristone in the luteal phase of women in the absence of any fall in progesterone levels (Swahn et al, 1988; Schaison et al, 1985) and also during pseudopregnancy in the presence of high levels of progesterone maintained by injections of hCG (Croxatto et al, 1985). In the monkey, there is a uniform sloughing of endometrium following luteal administration of mifepristone (Chillik et al, 1986). Sitruk-Ware et al noted a more patchy distribution of necrosis in human decidua, particularly when mifepristone had failed to induce abortion. In these cases, necrosis was localised to areas surrounding blood vessels (Sitruk-Ware et al, 1990). Schindler et al studied the ultrastructure of human decidua obtained by vacuum aspiration and found that necrosis of capillary endothelial cells was more common following mifepristone than in controls. In addition, they noted hyperplasia of the endoplasmic reticulum of the endothelium of decidual capillaries (Schindler et al, 1985). Similar ultrastructural changes have been noted by Johannisson et al following midluteal administration of mifepristone. They found not only necrosis of capillary endothelial cells but also narrowing of the capillary lumen and a decrease in the area of adventitia. In common with Schindler's group, the endoplasmic reticulum of the endothelial cells revealed extensive dilatation. These changes suggested a direct effect of mifepristone on progesterone primed endometrium which could lead to a decrease in the blood supply of the endometrium and therefore account for endometrial bleeding in the absence of luteolysis (Johannisson et al, 1989). Li et al and Swahn et al have also noted necrosis of the capillaries of midluteal mifepristone treated endometrium with the former group reporting leukocyte infiltration and apoptosis (Li et al, 1988; Swahn et al, 1988).

Progesterone receptors have been demonstrated in the endothelial cells of decidual blood vessels (Wang et al, 1992) and immunohistochemical staining of mifepristone exposed decidua reveals increased staining for the oestrogen receptor and progesterone receptor in the decidual vessels of the decidua parietalis suggesting that this may be the primary target for mifepristone (Shi et al, 1992; Shi et al, 1993). Cheng et al have shown that levels of prostaglandin dehydrogenase (PGDH) are reduced in decidual vessel walls after mifepristone treatment in vivo with a consequent increase in the local concentration of PGE2 (Cheng et al, 1993a; b). This further suggests a vascular target for the antigestagen. It is of interest that the endoplasmic reticulum calcium pump had been proposed as a non-genomic site of action of mifepristone in vitro in human myometrium (Lobaccaro-Henri et al, 1996) when the ultrastructural decidual changes described by both Schindler and Johannisson are considered (Schindler et al, 1985; Johannisson et al, 1989).
The myometrium is sensitised to exogenous prostaglandins when mifepristone is administered in early pregnancy and the clinical evidence for this will be reviewed later. The mechanism of this action of mifepristone on the myometrium, in common with the relaxant influence of progesterone, is not fully understood but it may in part be mediated by endogenous prostaglandins.

Progesterone is a potent inhibitor of prostaglandin synthesis in vitro (Abel & Baird, 1980; Kelly & Smith, 1987) in addition to increasing the metabolism of prostaglandins (Abel & Kelly, 1983). In early pregnancy there is a low synthetic capacity for prostaglandin production by decidual from both intra and extra uterine pregnancy (Maathius & Kelly, 1978; Abel et al, 1980). Inhibition of prostaglandin synthesis by progesterone has been demonstrated in vitro with rat myometrial explants and it has been shown that this can be overcome by mifepristone (Jeremy & Dandona, 1986). Although in vitro incubations of human decidual cells and explants with mifepristone have shown a modest increase in prostaglandin production (Smith & Kelly, 1987; Kelly & Smith, 1987), in vivo there is no increase in the peripheral plasma concentration of prostaglandin metabolites following oral administration of mifepristone (Hill et al, 1990a). In the pregnant guinea pig in vivo administration of mifepristone significantly reduces the subsequent in vitro ability of the chorion, myometrium and decidua to metabolise prostaglandins to their inactive metabolites (Kelly & Buckman, 1990) and in vivo administration of mifepristone to women in early pregnancy increases the PGE:metabolite ratio of cultured decidual explants when compared to control tissue (Norman et al, 1991b).

Prostaglandin dehydrogenase (PGDH), the enzyme which catalyses the catabolism of prostaglandin to its inactive metabolites, is under progesterone control (Falkay & Sas, 1978) with negligible levels in non-pregnant, proliferative endometrium (Casey et al, 1980) and high levels in early pregnant decidua (Kierse, 1985). Treatment with mifepristone in vivo significantly reduces the concentration of PGDH in first trimester decidua (but not chorionic villi) with a disappearance of the enzyme from around blood vessels of the decidua (Cheng et al, 1993a). In addition, PGE concentrations are increased in the perivascular region of the decidua after in vivo treatment with mifepristone (Cheng et al, 1993b).

These findings of a decrease in PGDH activity and a reduced catabolism of prostaglandin in early pregnant human decidua, provide a mechanism for a lower threshold for uterine stimulation, by exogenous oxytocics following mifepristone ingestion. They also explain why there is no increase in peripheral plasma levels of
prostaglandin metabolites after mifepristone administration (Hill et al., 1990a). The demonstration of perivascular changes in PGDH and PGE after mifepristone treatment suggests that mifepristone aids the passage of primary prostaglandins from the decidua to the myometrium and may also cause vasodilatory changes in the decidua.

It has become clear that the myometrial effects of mifepristone are not solely mediated by endogenous prostaglandins or other oxytocics. Norman et al. demonstrated a lack of inhibition of mifepristone stimulated uterine activity in early human pregnancy by indomethacin, a prostaglandin synthetase inhibitor (Norman et al., 1991a). Arkarvichien and Kendle found that myometrial activity in pregnant rats given mifepristone, increased before the concentration of uterine PGE\textsubscript{2} and PGF\textsubscript{2α} increased (Arkarvichien & Kendle, 1992). Chwalisz et al., studying the effects of onapristone on late pregnant guinea pigs found an increased response to exogenous oxytocin in the absence of any increase in the concentration of myometrial oxytocin receptors. This finding was associated with a marked increase in myometrial gap junctions (Chwalisz et al., 1991).

Myometrial gap functions are essential for the generation of co-ordinated uterine activity and are known to be influenced by the hormonal profile with progesterone exerting an inhibitory influence on gap junction numbers (Mackenzie & Garfield, 1985). Prostaglandins exert an influence on myometrial gap junctions with some exerting a stimulatory effect and others an inhibitory one (Garfield et al., 1980). Mifepristone increases the number of gap junctions between myometrial cells in pregnant rats (Garfield & Baulieu, 1987) and levels of transcripts encoding for Connexion-43 (the myometrial gap junction protein) were significantly increased in rat myometrium and associated with preterm delivery after treatment with mifepristone (Petrocelli & Lye, 1993).

While this myometrial effect of mifepristone would seem to be consequent to its action on the progesterone receptor, there is evidence of non-genomic, membrane effects of mifepristone on myometrium. Mifepristone has a relaxant effect, similar to progesterone and its metabolites, inhibiting spontaneous myometrial contractions of isolated rat myometrium. In addition, mifepristone antagonises calcium induced contractions in depolarised myometrial explants, suggesting that the antigestagen blocks calcium influx through the membrane channels. This \textit{in vitro} relaxant effect of mifepristone is short-lived and an increase in contractility is seen after five minutes incubation (Perusquia & Kubli-Garfias, 1994).
A similar agonistic, non-genomic, membrane interaction of mifepristone has been described by Lobaccaro-Henri et al, using non-pregnant human myometrial strips. They found that mifepristone rapidly reduced spontaneous uterine contractile frequency in a similar manner to the progesterone agonist R 5020 and dexamethasone. At the same time, prostacycline (PGI2) release was reduced in a dose-dependent manner and this was not found with superfusion of agonist or dexamethasone (Lobaccaro-Henri et al, 1992). As well as inhibiting PGI2 release from the myometrium, mifepristone was found to inhibit intracellular calcium mobilisation but did not oppose the contractile effects of vasopressin indicating that this agonist uses different sources of calcium from mifepristone. The rapid onset and reversal of these effects suggest a membrane effect of mifepristone and, thus, short-term actions of the antigestagen are not related to its antihormonal activity (Lobaccaro-Henri et al, 1996).

Mifepristone exerts an effect on the cervix, significantly increasing ripeness (Rädestad et al, 1988) and dilatation (WHO, 1990) when compared with placebo. This softening effect does not appear to be mediated by prostaglandins. Mifepristone does not increase the ability of cervical tissue in vitro to synthesise prostaglandin (Rädestad et al, 1990) and pretreatment with naproxen has no impact on the cervical softening effect of mifepristone in the early first trimester (Rädestad & Bygdeman, 1992). Mifepristone has been shown to increase the number of α2 adrenoceptors in the first trimester cervix (Kovacs & Falkay, 1993) and to influence cytokine activity (Chawlisz & Garfield, 1996).

The mechanism by which mifepristone induces abortion is unclear. Unlike Csapo's studies of lute-ectomy in early pregnancy, vaginal bleeding tends to precede any fall in ovarian steroid levels (Swahn et al, 1985; WHO, 1989). In vivo studies (Swahn et al, 1985; WHO, 1989) have failed to confirm in vitro observations of a direction suppression of trophoblastic synthesis of βhCG and progesterone (Bischof et al, 1986; Das & Catt, 1987) and histologically mifepristone does not appear to affect the trophoblast (Schindler et al, 1985). It seems probable that it is a composite of the effects of mifepristone on decidua, cervix and myometrium.

Although the development of mifepristone provided an effective agent for medical withdrawal of progesterone, clinical trials proved disappointing when it was used as an abortifacient. Herrman et al conducted the first trial attempting to induce abortion in 11 women of between six and eight weeks gestation with 200 mg of mifepristone daily for four days. Eight women aborted completely, one woman aborted incompletely and required haemostatic uterine curettage and two women had continuing pregnancies. Although the 73% complete abortion rate was low in
comparison with prostaglandin analogues, the reported incidence of side-effects was far less (Herrman et al, 1982).

Kovacs et al studied 37 women of less than 42 days amenorrhoea. They received either 25 mg, 50 mg, or 100 mg of mifepristone twice a day for four days. One woman was found to have an ectopic pregnancy and excluded from the subsequent analysis. Of the remaining 36 women, 22 (61%) aborted completely, 12 (33%) aborted incompletely and 3 (6%) had continuing pregnancies. Two of the women with incomplete abortions required emergency curettage and blood transfusion (Kovacs et al, 1984).

Couzinet et al reported the findings of the first large series of mifepristone-induced terminations. Using 400 mg to 800 mg of mifepristone over two to four days, complete abortion was induced in 85 of the 100 women treated. Recruitment criteria were stringent and inclusion depended on a pretreatment plasma βhCG of less than 18000 mU/ml and amenorrhoea less than five weeks. Fifteen women were judged not to have responded to mifepristone and 18 were noted to have a significant fall in the level of haemoglobin. Almost one quarter of those studied complained of nausea and fatigue during treatment but no pretreatment comparison was made. Pelvic pain was not a clinical problem (Couzinet et al, 1986).

Further studies examined the effect of lengthening the treatment period to seven days (Shoupe et al, 1986; Mishell et al, 1987; Birgerson & Odlind, 1987; 1988), varying the dose of mifepristone given (from 200 mg daily to 400 mg daily) (Shoupe et al, 1986; Mishell et al, 1987; Birgerson & Odlind, 1988; Sitruk-Ware et al, 1990) and adding ergometrine-like drugs to the treatment regime (Mishell et al, 1987; Grimes et al, 1990). With a few exceptions, the outcome of treatment with mifepristone in the early first trimester of pregnancy remained relatively constant and dose independent, confirming the findings of the early small trials. Van Look and Bygdeman reviewed treatment outcome with mifepristone in early pregnancy studies and obtained a mean of 62.5% complete abortions in women of less than 56 days amenorrhoea (Van Look & Bygdeman, 1989). The percentage of continuing pregnancies was relatively constant (between 10 and 30%) and the addition of ergometrine-based drugs neither increased expulsion rates nor decreased blood loss when abortion was incomplete (Mishell et al, 1987; Grimes et al, 1990). Using a large, single dose of mifepristone (400 - 600 mg) in an attempt to increase plasma concentrations of free, unbound drug, Baulieu and Ulmann and later Ylikorkala et al, simplified the treatment regime but failed to improve complete abortion rates (Baulieu & Ulmann, 1986; Ylikorkala et al, 1989). In most of these
studies when cortisol was measured, its plasma level was found to rise during treatment, reflecting a compensation for the antiglucocorticoid effect of mifepristone. Anaesthetic difficulties resulting from mifepristone's antiglucocorticoid action have not been reported so far despite initial fears (Healy, 1985).

Although there was no apparent relationship between successful outcome of treatment with mifepristone and the treatment regime employed, there did appear to be a correlation between success and gestation. Ulmann obtained a similar complete abortion rate to Couzinet (84% complete abortions) when treatment was limited to the first six weeks of amenorrhoea. When an identical 600 mg single dose of mifepristone was administered to women between six and eight weeks of amenorrhoea, the complete abortion rate fell to 58% (Ulmann, 1987). Two studies have specifically addressed the predictors of success of treatment with mifepristone in early pregnancy and have concluded that the level of hCG (and by inference gestation) at the time of treatment is an important determinant of outcome. Grimes et al found that the risk of failure was tripled once hCG levels exceeded 19800 mU/ml (Grimes et al, 1990; Sitruk-Ware et al, 1990) and Van Look and Bygdeman in their review of first trimester abortion using mifepristone obtained an 85% complete abortion rate for treatment in studies limited to the first 10 days after the missed period, falling to 62.5% in studies of women up to 56 days from their last period and plummeting to 35% when Vervest and Haspel's study group of 56 to 70 days amenorrhoea was considered (Van Look & Bygdeman, 1989; Vervest & Haspels, 1985). More recently administration of 600 mg mifepristone within 72 hours of unprotected intercourse has been shown to effectively prevent pregnancy, presumably by a direct effect of the antigestagen on the endometrium, disrupting implantation. Glasier et al compared 600 mg of mifepristone with the standard Yuzpe regimen of ethinyl oestradiol and norgestrel given within 72 hours of intercourse. Four hundred and two women received mifepristone, 167 within three days of ovulation. Twenty three pregnancies were predicted had no treatment been given. However, mifepristone was 100% effective in preventing pregnancy (Glasier et al, 1992). Webb et al compared the same mifepristone treatment regime with the Yuzpe regime and Danazol (200 mg x 3 within 72 hours of intercourse, repeated after 12 hours) and reported no pregnancies in the 195 women receiving the antigestagen (Webb et al, 1992).

Birgerson and Odlind have compared mifepristone with epostane for the induction of early abortion and found that treatment outcome is similar; both drugs are well
tolerated (although epostane appears to cause more nausea) and induce few side effects; both drugs are limited in their usefulness as abortifacients by a high incidence of incomplete abortion and continuing pregnancy (Birgerson & Odlind, 1987).

Elger et al have reported a synergistic effect of epostane and mifepristone and onapristone in the induction of delivery in guineapigs which was reversed by oestrogen and androstenedione but not by progesterone. In addition, tamoxifen was found to act synergistically with mifepristone in mid-pregnant guinea pigs (Elger et al, 1990). The addition of tamoxifen to a treatment regimen of mifepristone and 15-methyl-prostaglandin F₂α methyl ester in early human pregnancy did not confirm this synergism in women with tamoxifen treated women taking longer to pass products of conception (Van Look & von Hertzen, 1993). Lilopristone (ZK 98734) appears to have a greater abortifacient potential than mifepristone in animal models (Elger et al, 1990) but its efficacy does not differ from that of mifepristone in the human female. Kovacs et al, in a dose finding study of women of less than 49 days amenorrhoea found a complete abortion rate of 77% in a group of 30 women receiving 100 mg of ZK 98734 daily for four days (Kovacs et al, 1988). Swahn et al found a 68% complete abortion and 20% continuing pregnancy rate when 96 women of less than 49 days amenorrhoea were treated with a variety of doses of lilopristone (Swahn et al, 1994). Induction of early abortion with mifepristone is not complicated by the gastrointestinal side effects and pain that accompany treatment with prostaglandin analogues but the high failure rate means that this method of medical termination of early pregnancy does not provide an alternative to vacuum aspiration. It was found, however, that the addition of prostaglandin to treatment with mifepristone greatly increased the abortifacient efficacy of the antigestagen.

Bygdeman and Swahn were the first to demonstrate clinically the ability of mifepristone to sensitise the early pregnant uterus to exogenous prostaglandins. Complete abortion was induced in 32 (94%) of 34 women of less than 49 days amenorrhoea using either 50 mg or 100 mg of mifepristone daily for four days and a single 0.25 µg intramuscular injection of sulprostone on the fourth treatment day (Bygdeman & Swahn, 1985). The same dose regime of mifepristone without the addition of prostaglandin had yielded only a 61% complete abortion rate in a previous study (Kovacs et al, 1984). Only three women (9%) experienced severe pain and there was no increase in the incidence of vomiting or diarrhoea during treatment. It was felt that blood loss was less using this combination of mifepristone and prostaglandin than with the antigestagen alone. However, no objective measure of blood loss was made. There was no fall in haemoglobin concentration subsequent to treatment.
Cameron et al obtained identical outcomes using a similar treatment method. Treatment of 20 women receiving 150 mg mifepristone daily for four days was compared with treatment using the same regimen of mifepristone with the addition of a 1 mg gemeprost vaginal pessary on day 3 in 19 women. All women were less than 56 days from their last menstrual period. Ninety five per cent of women receiving additional prostaglandin, aborted completely. There was no increase in the incidence of vomiting, nausea or diarrhoea in either group and only three women (16%) in the combination group required intramuscular analgesia. Blood loss was measured in a number of women from each group and it was found that there was no significant difference in measured blood loss (Cameron et al, 1986). When these women were compared to the same population of women receiving either prostaglandin (gemeprost) alone or undergoing vacuum aspiration under general anaesthesia, the percentage of women aborting completely was only significantly different in the group receiving mifepristone alone. Although the use of gemeprost alone to induce abortion was as effective as the combination of mifepristone and gemeprost significantly more women experienced gastrointestinal side effects and 53% required intramuscular opiate analgesia (Cameron & Baird, 1988).

These early studies indicated that the addition of a small dose of prostaglandin analogue to treatment with mifepristone dramatically improved complete abortion rates in early pregnancy. This method of medical termination was objectively acceptable in terms of the low incidence of side effects, in particular the low incidence of severe pain. In addition, not only was it effective but it was also non-invasive. The combination of mifepristone with prostaglandin provided the first realistic alternative to vacuum aspiration as a method of early abortion.

In Chapter 2, efficacy of treatment with three single dose regimes of mifepristone, in combination with a prostaglandin analogue is examined and side effects considered. In Chapter 3 the effects of varying the dose of prostaglandin analogue used in combination with a single dose of mifepristone are assessed.

It has been suggested by Csapo that early abortion subsequent to administration of prostaglandin is not provoked solely by the oxytocic properties of these agents. He demonstrated in studies of induction of early abortion with prostaglandin (Csapo et al, 1972; Caspo et al, 1973c; Csapo & Pulkkinen 1979) that a fall in the level of progesterone (and oestradiol) preceded cervical dilatation and sustained uterine activity. Based on this and other work (Csepli & Csapo, 1975; Pulkkinen et al, 1975) he proposed a mechanism of abortion with prostaglandins.
Csapo hypothesised that the normally "refractory" early pregnant uterus could not respond to exogenous oxytocic agents without an initial change in the regulatory balance of uterine activity which usually maintains the uterus in a quiescent state (Csapo, 1977). Following administration of prostaglandins, the conceptus is compromised by prostaglandin-induced vasoconstriction (Csepli & Csapo, 1975; Pulkkinen et al, 1975) and this leads to a reduction of luteotrophic support of the corpus luteum. The subsequent progesterone withdrawal is followed by endogenous prostaglandin release and cervical dilatation. The regulatory imbalance caused by the fall in progesterone levels allows myometrial cells to respond more efficiently to lower prostaglandin concentrations, effectively sensitising the uterus to exogenous oxytocic (Csapo & Pulkkinen, 1979).

In Chapter 4, the mechanism of abortion in early pregnancy with both prostaglandin analogue and mifepristone, in combination with prostaglandin analogue is investigated by measurement of uterine contractility.

**Medical Abortion and Bleeding.**
As discussed earlier, the suitability of any method of medical termination of early pregnancy is dependent on its efficacy, acceptability and safety in comparison to vacuum aspiration. When considering the latter two attributes, attention must be paid both to the duration of bleeding following treatment and to the amount of bleeding induced.

The duration of bleeding following vacuum aspiration, although subjectively determined by women as shorter than that following termination with prostaglandins (Rosen et al, 1979), is in fact very similar. Bleeding following prostaglandin induced early abortion invariably continues for between one and two weeks (Mackenzie et al, 1978; Bygdeman et al, 1980a; 1981; 1983; World Health Organization 1982a; Bygdeman & Van Look, 1989).

Comparative studies of prostaglandin and vacuum aspiration have shown little difference in the duration of bleeding following either method of abortion, with the surgical group also bleeding for one to two weeks following treatment (Rosen et al, 1979; Smith & Baird, 1980; Cameron & Baird, 1988; Baird et al, 1988). Bleeding following mifepristone with or without additional prostaglandin, also continues for an average of one to two weeks after early abortion (Couzin et al, 1986; Cameron et al, 1986; Bygdeman & Van Look, 1989). In terms of the patient acceptability of the duration of blood loss following abortion, there is no difference between surgical and medical methods.
In most studies of first trimester medical abortion, treatment is restricted to the first eight weeks of pregnancy, partly because of the subjective perception that heavy bleeding in connection with medical abortion is more frequent with increasing gestation (Bygdeman, 1984). Women subjectively assess blood loss following medical termination as greater than that following vacuum aspiration despite no demonstrable differences in haemoglobin levels (Rosen et al, 1979; WHO, 1982) and educated intervention based on subjective analysis of blood loss can be just as inaccurate with a 50% emergency curettage rate in one study group receiving mifepristone with no subsequent significant fall in haemoglobin being detected (Shoupe et al, 1986). Subjective measurement of vaginal blood loss is well accepted to be a poor indicator of actual blood loss (Barer & Fowler, 1939; Hyten et al, 1964; Jacobs & Butler, 1965; Hallberg et al, 1966; Fraser et al, 1984). However, few studies of early medical abortion have objectively measured blood loss. Where blood loss has been measured in abortion studies, the alkaline haematin method, or modifications of it, has been used for quantification (Hallbert & Nilsson, 1964; Newton et al, 1977). Although the aesthetic disadvantages of this technique are considerable for the investigator, it is a simple, non-invasive and cheap alternative to methods involving prelabelling of the woman's red blood cells with radioisotopes (Baldwin et al, 1961; Jacobs & Butler, 1965; Holt et al, 1967). Pictorial blood loss assessment charts have been used in the assessment of menorrhagia in an attempt to avoid collection and analysis of towels and tampons (Higham et al, 1990) but their usefulness is limited by inaccuracy (Deeny & Davis, 1994).

The alkaline haematin method provides an accurate measure of blood loss (Shaw et al, 1972; Cameron, 1987). However, in the case of menstruation, blood does not constitute the only fluid and when total menstrual loss is considered by weighing of sanitary towels, the haematin element may contribute only 36% of loss (Fraser et al, 1985). This could be assumed to follow for vaginal loss subsequent to abortion, when fluid from the gestational sac must increase the total volume of loss, and provides some explanation for the apparent discrepancy between perceived and actual blood loss following abortion. Although the alkaline haematin method does not measure the total loss, it does measure the haematin element and it is this constituent that is relevant to the development of anaemia and to the safety of the abortion method used.

Hamberger et al measured blood loss during and following induction of abortion in 37 women of less than 56 days amenorrhoea with 15-methyl PGF$_{2\alpha}$ vaginal pessaries. They found a mean loss of 37 mls over the first 24 hours of treatment and
94 mls for remaining duration of bleeding (up to 25 days). Heavy blood loss correlated with a slow decline in the level of hCG following abortion. However, only four women had a measured loss of greater than 200 mls (Hamberger et al, 1978). This total mean blood loss of 121 mls is higher than that recorded during other studies of prostaglandin induced early abortion. However, it may be explained by the use of an F series analogue rather than E series as in the other studies.

Bygdeman et al, measured blood loss in 10 of 40 patients treated with meteneprost in early pregnancy and found a mean loss of 78 mls (30 to 150 mls range) over 12 days (7 to 22 days range). The highest daily loss occurred within the first four days of treatment (Bygdeman et al, 1981). In a further study blood loss was measured in 20 women following meteneprost. The findings were similar with a mean loss of 61.7 mls (21 to 150 mls range) and the highest daily loss occurring within the first four days (Bygdeman et al, 1983).

Smith and Baird, in a study comparing early abortion using gemeprost with vacuum aspiration, performed under general or local anaesthesia, found a total mean blood loss of 87 mls with prostaglandin, 72 mls with vacuum aspiration under local and 85 mls with vacuum aspiration under general anaesthesia. Of interest, the post-induction blood loss, ie. blood loss after the first 24 hours, was significantly higher in the prostaglandin treated group - 69 mls versus 35 mls (Smith & Baird, 1980). This provides another explanation for women's perception that more blood is lost during and after medical abortion.

Kovacs et al found a mean of 87 mls blood loss following induction of abortion with mifepristone (Kovacs et al, 1984). Cameron et al reported a lower loss of only 53 mls. However, when women who subsequently underwent surgical evacuation of uterus were excluded from analysis, the median loss rose to 62 mls (42 mls to 227 mls range). Women receiving a combination of mifepristone and prostaglandin were also considered in this study and were found to have similar blood loss: 81 mls [(32 mls to 222 mls range)] (Cameron et al, 1986).

In Chapter 5, blood loss following induction of early abortion with mifepristone and a prostaglandin analogue is investigated.
Midtrimester Abortion.
Midtrimester abortions account for a decreasing minority of therapeutic pregnancy terminations in Scotland. Only 6.1% of abortions in Scotland in 1995 were performed after 13 weeks, a fall of more than 5% from 1985 (Scottish Office, Department of Health, 1996). However, second trimester abortions account for a disproportionate amount of morbidity and mortality related to abortion. Morbidity increases by 15 to 30% for every week of delay after eight weeks (Cates & Grimes, 1981) and the risk of major complications doubles between 8 and 15 weeks gestation (Filshie, 1989). Death as a direct result of abortion is 25 times more likely between 16 to 20 weeks gestation than before eight weeks (Tyler, 1981).

Although surgical methods for evacuation of the mid-pregnant uterus predominate in the private sector in England and Wales, induction of abortion with prostaglandins is the most widely used second trimester abortion technique within the National Health Service (Stanwell-Smith, 1984), with 87% of abortions after 13 weeks being performed this way in Scotland in 1990 (Scottish Home & Health Department, 1991). Unlike induction of early abortion, success of midtrimester abortion techniques does not depend on an endpoint of complete abortion. Studies of prostaglandin induced midtrimester abortion vary greatly in the reported incidence of complete and incomplete abortion, reflecting individual practice rather than efficacy of the method.

As discussed earlier, systemic (intravenous, intramuscular, oral, vaginal) administration of prostaglandins $E_2$ and $F_{2\alpha}$, although effective in the induction of abortion at all gestations, is limited in its clinical usefulness by a high incidence of dose-related prostaglandin side effects - in particular vomiting, diarrhoea and pain. Extra-amniotic delivery of prostaglandins $E_2$ and $F_{2\alpha}$, however, causes fewer side effects because the local action of these agents allow the effective use of much smaller doses of prostaglandin. Although, as reviewed previously, this technique is not suited to early pregnancy, extra-amniotic delivery of prostaglandin $E_2$ by repeated injection (Embrey & Hillier, 1971; Embrey et al, 1972; Wiqvist et al, 1972) or continuous infusion (Miller et al, 1972) is an efficient method of midtrimester abortion with around 85% of women aborting with prostaglandin alone and almost 100% if oxytocin is used in addition (Bygdeman, 1984). The major limitation of the method is the need for repeated instillations and for the presence of an indwelling catheter.
Attempts to overcome this by a single large dose of prostaglandin have been unsuccessful in the second trimester of pregnancy with 40% of patients having accidental rupture of the membranes during instillation of the initial dose (Bygdeman, 1981).

An alternative local route of prostaglandin administration in the second trimester of pregnancy is intra-amniotic injection. Although intra-amniotic instillation of glucose, hypertonic saline and urea had all been described prior to the use of prostaglandins for abortion, they had distinct limitations. Glucose was found to be associated with a high risk of infection and a prolonged interval until abortion (Burnett et al, 1974; Droegemuller & Greer, 1970). Hypertonic saline induced abortion in around 95% of women but, as with glucose, the interval to abortion was lengthy (Brenner, 1975; Schulman et al, 1971) and hypernatraemia (Brenner, 1975; Kerenyi et al, 1973; Burnett et al, 1974) and coagulopathy (Brenner, 1975; Cohen & Ballard, 1974) were identified as specific risks of the method. Urea was found to be less potent than hypertonic saline, though less likely to cause serious complications (Weinberg et al, 1975), and required augmentation with oxytocin or laminaria (Brenner, 1975; Burnett et al, 1974).

The use of intra-amniotic injection is restricted to a gestation when transabdominal puncture of the amniotic sac is relatively uncomplicated ie. after 14 or 15 weeks gestation. Following intra-amniotic injection, prostaglandins have a more prolonged duration of action than when extra-amniotically administered. Because amniotic fluid lacks the enzymes required to metabolise prostaglandin, the injected prostaglandin forms an intra-amniotic reservoir (Toppozada, 1986). The initial metabolism of intra-amniotic prostaglandin, as it is slowly transferred across the fetal membranes to maternal plasma, is similar to, though much slower than, intravenously injected prostaglandin. Intra-amniotic prostaglandin F2α has a half life of approximately 12 to 20 hours (Pace-Asciak et al, 1972; Granström et al, 1973).

Early studies of intra-amniotic injection revealed that doses of 5 to 25 mg of PGF2α required repetition to produce success rates equivalent to extra-amniotic prostaglandin E2 (Toppozada et al, 1971; Karim & Sharma, 1971c) over a 48 hours treatment period. An initial dose of 25 mg PGF2α repeated if necessary 24 hours later, yielded a 90 to 95% abortion rate with an induction abortion interval of approximately 30 hours. This interval could be reduced to around 20 hours by repeating the dose six hours rather than 24 hours following the initial injection with no reduction in success (Bygdeman et al, 1973; WHO, 1976). Attempts to simplify the procedure by giving a single 40 mg (Wiqvist et al, 1973) or 50 mg (Brenner et al, 1973;
Corlett & Ballard, 1974; Lauersen & Wilson, 1974) intra-amniotic injection of PGF$_{2\alpha}$ resulted in 95% and 85% abortion rates respectively in small trials. A large multicentre trial was less encouraging, with 86% of 351 patients receiving 50 mg intra-amniotic PGF$_{2\alpha}$ aborting within 48 hours and 81% of 251 of those receiving 40 mg of intra-amniotic PGF$_{2\alpha}$. Only 67% of the 50 mg group and 54% of the 40 mg group aborted within the first 24 hours of treatment (WHO, 1977b). The incidence of gastrointestinal side effects of single or multiple intra-amniotic injections of PGF$_{2\alpha}$ was in general higher than that associated with extra-amniotic PGE$_2$ though lower than with systemically administered prostaglandin (Bygdeman, 1981). Prostaglandin E$_2$ 5 mg given intra-amniotically every 10 hours to a maximum of four injections induced abortion in over 90% of women in one trial (Karim et al, 1972) and the addition of intra-amniotic urea to 2.5 mg of intra-amniotic PGE$_2$ was shown to significantly reduce the mean induction abortion interval from around 20 hours to 15 hours (Craft, 1975).

In comparison with intra-amniotic hypertonic saline, intra-amniotic PGF$_{2\alpha}$, either as a single 50 mg injection or 6 hourly 25 mg injections, causes more gastrointestinal side effects but has a significantly shorter induction-abortion interval. Edelman et al studied 372 women of 15 to 20 weeks gestation randomised to receive a single 50 mg intra-amniotic injection of PGF$_{2\alpha}$, multiple 25 mg injections of PGF$_{2\alpha}$ (at 0, 6, 24 and 30 hours if required) or 200 mls of 20 g/dl saline solution. Cumulative abortion rates at 72 hours were similar in all groups with over 90% of women aborting. However, significantly more women in the prostaglandin groups aborted within the first 24 hours and the mean induction abortion intervals were far lower in the prostaglandin treated women: 17.4 hrs (multiple 25 mg PGF$_{2\alpha}$, 20.4 hrs (50 mg PGF$_{2\alpha}$) compared with 26.3 hours (hypertonic saline) (Edelman et al, 1976).

The World Health Organization Task Force on Prostaglandins studied 717 women given two 6-hourly intra-amniotic injections of PGF$_{2\alpha}$ and 796 women given hypertonic saline. The results were similar to those of Edelman et al with the prostaglandin group experiencing more gastro-intestinal side effects but having a shorter time interval to abortion (WHO, 1976). Both these studies concluded that although the methods were equally safe, prostaglandin F$_{2\alpha}$ was a more efficient intra-amniotic abortifacient by virtue of its greatly reduced induction-abortion interval.

Although extra- and intra-amniotic prostaglandins E$_2$ and F$_{2\alpha}$ effectively induce midtrimester abortion, their invasive route of administration is associated with certain risks. As discussed earlier, inadvertent intravenous injection of extra-amniotic
prostaglandin E2 can cause adverse reactions (McNicol & Gray, 1977). Collapse (Cameron & Baird, 1984a) and death (Cates & Jordan, 1979) have been reported following intra-amniotic instillation of prostaglandins. Cervical rupture or tearing has been reported as a complication of intra-amniotic prostaglandin instillation, particularly when oxytocin is infused simultaneously (Wentz et al, 1973; Kajanoja et al, 1974; Bradley-Watson & Craft, 1974). However, it seems more likely that this is a non-specific phenomenon complicating intra-amniotic infusion of both hypertonic saline and prostaglandin in the presence of an unripe, usually primiparous cervix (WHO, 1976; Bygdeman, 1984). Although intra-amniotic prostaglandin F2α has been cited as a cause of epileptic seizure (Lynham et al, 1973), other investigators have not substantiated this claim (Craft, 1973; Fraser & Gray, 1974; Mackenzie et al, 1973). There is, however, a well accepted risk of seizure secondary to water-intoxication resulting from the prolonged infusion of oxytocin during induction of abortion (Grimes & Cates, 1979).

The development of the more stable and potent prostaglandin analogues provided potential for non-invasive induction of midtrimester abortion. 15-methyl PGF2α was the first analogue to be widely investigated in the second trimester. Early studies, however, concentrated on its intrauterine administration.

Wiqvist et al conducted a dose finding study investigating the efficacy of 1 mg, 2.5 mg or 5 mg of intra-amniotic 15-methyl PGF2α for induction of abortion in women between 15 and 20 weeks gestation. 2.5 mg 15-methyl PGF2α was found to be the optimal dose with 98% of 50 women aborting within 48 hours (versus 46% with 1 mg and 95% with 5 mg). The incidence of gastrointestinal side effects with this dose of the F analogue was less than with 40 mg of the parent compound (Wiqvist et al, 1973).

The WHO Task Force on Prostaglandins subsequently conducted a large multicentre comparative trial of 2.5 mg intra-amniotic 15-methyl PGF2α and 40 or 50 mg of PGF2α. Of the 919 women receiving 15 methyl PGF2α, 873 (95%) aborted within 48 hours with a mean induction abortion interval of between 18 to 20 hours. Seventy four per cent of these women aborted within 24 hours. Although intra-amniotic injection of the analogue was more effective than intra-amniotic injection of the parent compound, there was a much higher incidence of gastro-intestinal side effects. In addition, the risks of intra-amniotic instillation techniques were illustrated by a 3% incidence of cervical damage in all treatment groups (WHO, 1977b). Karim and Sivasamboo have suggested that, unlike Wiqvist et al (1973), a lower dose of intra-amniotic 15-methyl PGF2α can
significantly reduce side effects in particular cervical laceration, without compromising efficacy (Karim & Sivasamboo, 1975).

The greater stability of 15-methyl PGF\(_{2\alpha}\) means, as with its intra-amniotic instillation, that a single extra-amniotic instillation is sufficient to induce mid trimester abortion. Wiqvist et al induced abortion in 84% of 55 women with a mean induction-abortion interval of 13.6 hours using a mean dose of 730 \(\mu\)g of 15-methyl PGF\(_{2\alpha}\) (Wiqvist et al, 1974). In a large multicentre study, the WHO Task Force on Prostaglandins induced abortion in 80% of 660 women of 10 to 20 weeks gestation with a single 920 \(\mu\)g extra-amniotic injection of 15-methyl PGF\(_{2\alpha}\). The mean induction abortion interval was similar to that of Wiqvist et al: 14 hours and 73% of women aborted within 24 hours. Vomiting and diarrhoea were less frequent than with intra-amniotic injection but still experienced by 32 and 38% respectively (WHO 1977c). The finding that 15-methyl PGF\(_{2\alpha}\) could be administered by intramuscular injection without the inflammatory sequelae of the natural prostaglandins, stimulated hope for a non-invasive method of prostaglandin induced abortion. Early trials confirmed its efficacy as a second trimester abortifacient when given by this route but were unanimous in their reporting of unacceptable levels of vomiting and diarrhoea (Karim & Sharma, 1972; Bygdeman et al, 1974; Lauersen & Wilson, 1975).

The WHO Task Force on Prostaglandins treated 515 women of 10 to 20 weeks gestation with 200 \(\mu\)g followed three hours later by 300 \(\mu\)g of 15-methyl PGF\(_{2\alpha}\) repeated 3-hourly for up to 30 hours. Seventy nine per cent of women aborted in the first 24 hours, 85% within 30 hours and the mean interval to abortion was 14.7 hours. The incidence of diarrhoea and vomiting was found to be unacceptably high (WHO 1977a).

As discussed earlier, the methyl ester of this 15-methyl F analogue is stable in suppository fat and, therefore, suitable for vaginal administration. Bygdeman et al successfully induced abortion in 100% of mid trimester pregnancies using 1 or 2 mg 15-methyl PGF\(_{2\alpha}\) methyl ester pessaries given 3-hourly for 24 hours in a small trial (Bygdeman et al, 1976b). The WHO Task Force on Prostaglandins treated 310 women of 13 to 20 weeks gestation with 1.5 mg 15-methyl PGF\(_{2\alpha}\) methyl ester pessaries given 3-hourly for up to 24 hours. Although highly effective (with 88% aborting within 24 hours and 92% within 30 hours - mean induction - abortion interval 14.2 hours) the majority of women experienced vomiting and diarrhoea and the level of side effects was deemed as severe as that with the use of the intramuscular free acid (WHO, 1977d). Bygdeman et al were unsuccessful in their
attempt to reduce side effects by the use of a slow release device, with women receiving 15-methyl PGF$_{2\alpha}$ methyl ester in this manner, experiencing more side effects than those receiving 1.5 mg pessaries (Bygdeman et al, 1976c).

The use of a long-acting 3 mg pessary marginally improved gastro-intestinal problems (Bygdeman et al, 1977). However, this method of delivery compared unfavourably with intra-amniotic PGF$_{2\alpha}$ having a longer interval to abortion and a significantly higher incidence of vomiting and diarrhoea (Mandelin 1978).

The E series analogue 16,16 dimethyl PGE$_2$ was found to effectively induce midtrimester abortion when administered vaginally. Unlike 15 methyl PGF$_{2\alpha}$, it was not necessary to premedicate women with anti-emetic and anti-diarrhoeal compounds to allow gastro-intestinal tolerance (Martin et al, 1976). Unfortunately, its lack of long-term stability precluded its widespread use and it was not until the development of the stable E series analogues - sulprostone, meteneprost and gemeprost - that non-invasive administration of prostaglandin analogues became a practical alternative to midtrimester intrauterine techniques.

Karim et al induced abortion in 90% of 100 women in the second trimester of pregnancy with 0.5 mg sulprostone intramuscularly 4-hourly or 1 mg sulprostone intramuscularly 8-hourly. The incidence of gastro-intestinal side effects was low and comparable with those experienced with intra-amniotic hypertonic saline (Karim et al, 1978). Using the same treatment regime, the WHO Task Force on Prostaglandins found the lower dose to be less effective with 80% of women aborting. Eighty six of those receiving 1 mg injections aborted and the mean induction - abortion interval in both groups was 15 hours. Side effects were low and the incidence of vomiting and diarrhoea was felt to be within acceptable limits (WHO, 1982b).

Meteneprost, administered vaginally, was found to compare well with intramuscular sulprostone for the induction of midtrimester abortion. Bygdeman et al administered 75 mg meteneprost vaginally at 0 and 8 hours to 52 women of 15 to 24 weeks gestation. Seventy six per cent aborted within 24 hours and 83% within 30 hours. The addition of two hourly injections of 15-methyl PGF$_{2\alpha}$ to the regime after 24 hours resulted in a 100% cumulative abortion rate by 42 hours. The mean induction-abortion interval was 15.2 hours. Forty per cent of women vomited and 13% experienced diarrhoea and it was felt to compare favourably with 15-methyl PGF$_{2\alpha}$ with the incidence of gastro-intestinal side effects being about half those found with the F analogue by the same group. The main problem was a 25% incidence of hyperthermia (Bygdeman et al, 1980b).
Ballard studied 37 women of 10 to 16 weeks gestation following a 75 mg or 60 mg dose of meteneprost repeated after 8 hours. Although 86% of women receiving the higher dose aborted within 24 hours, only 53% of women receiving the lower dose did so. The induction - abortion interval was prolonged to 21.9 hours in the 60 mg compared with 14.7 hours in the 75 mg group. The incidence of vomiting and diarrhoea was low (18% and 0% respectively). However, 59% of women had a temperature elevated above 38°C (Ballard, 1981). Gemeprost, also administered in vaginal pessary form, was found to produce very similar results. Early trials reported an 87 to 95% abortion rate in the midtrimester with 3-hourly administration of up to 5, or in one case (Takagi et al, 1982), 10, 1 mg pessaries. However, the study groups included abnormal pregnancies (intrauterine deaths, molar pregnancies and threatened abortions), in addition to normal pregnancies (Wagatsuma et al, 1979; Takagi et al, 1982; Sakamoto et al, 1982).

Cameron and Baird compared the use of gemeprost pessaries with extra-amniotic infusion of prostaglandin E2. Using 3-hourly administration of up to 5 1 mg pessaries and 100 µg / hour infusion of PGE2 for up to 24 hours, abortion was induced in 77% (44 of 57) and 79% (46 of 58) women respectively within 24 hours. The induction abortion intervals were similar: 13.9 hours for the pessary group and 14.9 hours for the infusion group. There was no difference in the incidence of vomiting or diarrhoea but women treated with gemeprost required significantly less opiate analgesia (Cameron & Baird, 1984b).

In a further study, Cameron et al employed the same treatment regime described by Takagi et al (1982) using a second course of up to five 3-hourly administered 1 mg pessaries if abortion failed to occur within the first 24 hours. One hundred and thirteen women of 12 to 16 weeks gestation were studied. Eighty two per cent (93) aborted within 24 hours using a mean 4.4 pessaries. Sixteen of the 20 women who failed to abort with the first course, aborted during treatment with the second course of pessaries, giving an cumulative abortion rate of 96% for prostaglandin therapy alone. The majority of women required parenteral analgesia and the incidence of vomiting and diarrhoea (14% and 20% respectively) was not increased by the use of a second course of pessaries. The mean interval to abortion was 14.7 hours (Cameron et al, 1987). Prostaglandin E analogues have improved midtrimester prostaglandin abortion techniques by providing a non-invasive method of termination which causes fewer side effects - in particular, less vomiting and diarrhoea. Unfortunately, although more potent than their parent compound, their use does not reduce the time interval to abortion. Prostaglandins and their analogues whether given systemically or locally, invasively or non-invasively, fail to induce abortion in at
least 20% of women within 24 hours. One method of reducing the prostaglandin abortion interval is by pretreating the cervix with laminaria tent. Takagi et al pretreated 17 women of between 12 and 23 weeks with the insertion of laminaria which was removed 24 hours later prior to treatment with 0.25 or 0.5 mg gemeprost pessaries given 3-hourly. All patients had aborted by 7 hours using between 0.75 mg and 2 mg total gemeprost. Although this group of women included some with abnormal pregnancies (intrauterine death and threatened abortion) the induction abortion interval was half that of a similar group of women (with both normal and abnormal pregnancies) treated with a mean of 5 mg gemeprost but without cervical pretreatment (Takagi et al, 1982).

Karim et al demonstrated that pretreatment with laminaria for 12 to 18 hours prior to 4-hourly injections of intramuscular sulprostone both increased efficacy and reduced the side effects of treatment with the analogue in the second trimester (Karim et al, 1982). In a larger trial, Bygdeman and Christensen studied the effect of insertion of a medium sized laminaria 12 hours prior to treatment with either 0.25 mg 15-methyl PGF$_{2\alpha}$ two hourly intramuscularly or sulprostone 0.5 mg 4-hourly intramuscularly between 13 and 24 weeks gestation. Fifty five of 56 women (98%) aborted within 24 hours in the F analogue group and 63 of 64 (98%) aborted within 24 hours in the E analogue group. The prostaglandin induction abortion intervals were similar: around 10 hours. There were no cervical lacerations. The incidence of gastro-intestinal side effects was significantly lower in the sulprostone treated group and comparable with side effects associated with hypertonic saline instillation (Bygdeman & Christensen, 1983).

Thong and Baird failed to demonstrate any impact of pretreatment with a synthetic tent, dilapan, on the prostaglandin induction-abortion interval when using gemeprost 1 mg given 6-hourly between 12 and 18 weeks gestation. The median interval to abortion did not differ significantly between women who received dilapan priming and those who did not (15.6 and 15.7 hours respectively). Eighty five per cent of women receiving dilapan aborted within 24 hours (Thong & Baird, 1992a).

Selinger obtained a 50 to 70% reduction in the prostaglandin induction abortion interval following 24 to 72 hours pretreatment with epostane prior to extra-amniotic injection of 1.5 mg PGE$_2$ compared with controls who had received no pretreatment.

Although the numbers studied were small and results slightly conflicting, there was a suggestion of increased uterine response to exogenous prostaglandin following epostane pretreatment (Selinger, 1988).
Urquhart and Templeton studied the effects of pretreatment with 200 mg of mifepristone prior to extra-amniotic infusion of PGE₂, in 40 women between 16 and 18 weeks gestation. Twenty women received mifepristone and extra-amniotic prostaglandin and 20 women only extra-amniotic prostaglandin. The pretreated group aborted on average 9.2 hours after the start of the prostaglandin infusion and required 11 mg PGE₂ in total. The control group aborted 12.2 hours after the start of treatment using 18 mg PGE₂ in total (Urquhart & Templeton, 1987).

In summary, midtrimester pregnancy termination represents only a small proportion of abortions performed in the United Kingdom. However, the subsequent incidence of morbidity is high in comparison with early abortions. Although the introduction of non-invasive administration of prostaglandin analogues has helped to reduce, not only prostaglandin-related collapse and cervical injury, but also the incidence of gastro-intestinal side effects, induction of midtrimester abortion remains a long and painful procedure with a considerable number of women requiring more than 24 hours of treatment with prostaglandin. The combination of prostaglandin analogues with various pretreatment agents, appears to shorten the interval to abortion and in Chapter 6 the effects of pretreatment with mifepristone on induction of second trimester abortion with the prostaglandin analogue, gemeprost, are studied.
CHAPTER 2.

INDUCTION OF EARLY ABORTION WITH THREE DIFFERENT SINGLE DOSE REGIMES OF MIFEPRISTONE IN COMBINATION WITH A PROSTAGLANDIN ANALOGUE (GEMEPROST).
Introduction.
In Scotland 63% of the 11,143 legal abortions carried out in 1995, were performed in the early first trimester. With the exclusion of teaching centres with a research interest in medical methods of abortion, the majority were carried out by vacuum aspiration ((ISD, Scottish Office, Department of Health, 1996).

Although vacuum aspiration is a safe procedure it requires skilled medical and nursing staff and is most effective when performed under general anaesthesia (Tietze & Lewit, 1972). Complications of any method of abortion are related to the gestation at which it is performed with morbidity increasing with increasing gestation (Cates & Grimes, 1981). Surgical termination of pregnancy by vacuum aspiration is safest when performed between seven and 10 weeks gestation. However, complications, particularly incomplete evacuation, are increased before this gestation (Tietze & Lewit, 1972). Surgical abortion and its attendant problems can be avoided at this early stage of pregnancy by inducing abortion with prostaglandin analogues. Before eight weeks of pregnancy complete abortion can be induced in over 90% of women with prostaglandin analogues of the E series. A high incidence of prostaglandin related side effects, such as vomiting, diarrhoea and pain, limit the acceptability of these agents as an alternative to vacuum aspiration (Bygdeman et al, 1980a; Bygdeman et al, 1983).

Mifepristone causes fewer side effects than prostaglandin E series analogues when used to induce abortion before eight weeks of amenorrhoea but is a much less effective abortifacient with only 62% of women aborting completely (Van Look & Bygdeman, 1989). Two reports have suggested that efficacy of treatment with the antigestagen can be greatly improved, without a significant increase in the incidence of side-effects, by the addition of a small dose of prostaglandin analogue (Bygdeman & Swahn, 1985; Cameron et al, 1986). These reports describe the administration of mifepristone over a period of three (Cameron et al, 1986) or four (Bygdeman & Swahn, 1985) days prior to prostaglandin. This method of administration presents a practical problem in the United Kingdom. Under the provision of the 1967 Abortion Act, mifepristone can only be ingested in a hospital or on suitably licensed premises. Therefore, a sequential prescription of the antigestagen will involve three, if not four, days of hospital contact for women.

When mifepristone is used alone to induce abortion, sequential administration of the drug confers no advantage over a single large dose administration and abortion rates are comparable with the simplified prescription regime (Baulieu & Ulmann, 1986). In this Chapter the efficacy of a single 400 mg, 500 mg or 600 mg dose of
mifepristone followed 48 hours later by a gemeprost pessary for the induction of early abortion is studied in 80 women of less than 56 days amenorrhoea.

Methods.
Eighty women of less than 56 days amenorrhoea were recruited to this open study of 400 mg, 500 mg or 600 mg of mifepristone followed 48 hours later by a gemeprost pessary.

Recruitment.
Local Family Planning Centres and General Practitioners were asked to refer women of less than 56 days of amenorrhoea, requesting termination of pregnancy to the Gynaecological Out Patient Department of the Royal Infirmary of Edinburgh. Requests for termination of pregnancy were discussed and women counselled. A full history was taken and examination, including vaginal examination, was performed. Women with grounds for termination of pregnancy under the provision of the 1967 Abortion Act and who fulfilled the inclusion criteria of the study were offered the option of medical termination of pregnancy with mifepristone and gemeprost as an alternative to vacuum aspiration. Women were given a written information sheet and details of the study were discussed verbally. Written, informed consent was obtained from each woman prior to recruitment to the study which had been granted local Ethical Committee approval.

Exclusion criteria for the study were:
- age less than 16 years.
- more than 56 days amenorrhoea at the start of treatment.
- abnormal pregnancy including history of threatened abortion, non-viable pregnancy, ectopic pregnancy, multiple pregnancy.
- more than two previous spontaneous abortions.
- past or current medical history of serious respiratory, cardiovascular, gastrointestinal, genito-urinary, endocrine or neurological illness.
- specific contraindications to mifepristone or prostaglandin, including past or present use of systemic corticosteroids.

Following recruitment a detailed menstrual, past obstetric and medical history was taken. Women were asked specifically about the incidence of nausea, vomiting and diarrhoea or any other symptoms. Height, weight, blood pressure, pulse rate and temperature were recorded. Gestational age was assessed by pelvic ultrasound scan. Blood was taken for blood group typing and estimation of the concentration of haemoglobin and human chorionic gonadotrophin (hCG). An admission date was
arranged (usually within two days of recruitment) and women were issued with a diary in which to keep a record of the incidence of vomiting, nausea, diarrhoea, pelvic pain, vaginal bleeding or other symptoms. Entries in the diary were to commence on the day prior to admission.

**Treatment.**

On Day 1 of treatment, 30 consecutive women received a single, oral dose of 500 mg mifepristone (Group 1), 30 women received a single oral dose of 400 mg mifepristone (Group 2) and 20 consecutive women received a single oral dose of 600 mg mifepristone (Group 3). No dietary restrictions were imposed and tablets were swallowed with water.

Forty eight hours later, on Day 3 of treatment, prostaglandin was administered. The first six women in Group 1 were given a whole 1 mg gemeprost pessary inserted into the posterior fornix of the vagina. The following 74 women recruited to the study were given half of 1 mg gemeprost pessary with the remainder of the pessary being inserted only if vaginal bleeding or pelvic pain had not commenced within the first three hours of prostaglandin administration. Women remained supine for one hour following pessary insertion. Pessaries were halved with a scalpel. Prophylactic medication was not prescribed and analgesia was given as required. Oral paracetamol 1G was given for mild pain, oral dihydrocodeine 30 mg for moderate pain and intramuscular diamorphine 5 mg for severe pain. Intramuscular cyclizine 50 mg was given in treatment of vomiting. Women were advised not to self-medicate with non-steroidal anti-inflammatory preparations.

**Assessments.**

Women were questioned about the incidence of nausea, vomiting, diarrhoea, pelvic pain, vaginal bleeding (or any other symptom) immediately prior to mifepristone ingestion and hourly during the observation period following ingestion. Temperature, blood pressure and pulse rate were measured prior to and hourly following mifepristone for 10 hours in the first 10 women recruited and for two hours in the remaining 70 women. Women were then allowed home and instructed to keep a daily record of previously mentioned symptoms.

Immediately prior to prostaglandin administration and hourly following prostaglandin administration until discharge, women were questioned about the incidence of previously listed symptoms and measurements of temperature, blood pressure and pulse rate were made. All women remained in hospital for at least four hours following prostaglandin administration and prior to discharge a vaginal examination
was performed to exclude the presence of products of conception at the cervical os. Women were allowed home once pelvic pain and vaginal bleeding had settled and instructed to keep a daily record of previously listed symptoms. Blood group rhesus negative women received anti-D prophylaxis before discharge. Women were requested to use barrier methods of contraception until the onset of their first period post-abortion.

**Follow Up Visits.**
Women were reviewed 1, 2 and 4 weeks following treatment. At each visit the daily record of symptoms was reviewed and a history of any medical intervention taken. Vaginal examination was performed to assess uterine size and the state of the cervix. Blood was taken for estimation of haemoglobin concentration at the first visit and for estimation of the serum concentration of hCG at every visit. Abortion was considered complete if by four weeks vaginal bleeding had ceased, the uterus was normal sized, the cervix closed and the serum level of hCG was less than 400 mU/ml. Surgical evacuation of the uterus was performed when a diagnosis of incomplete abortion was made.

**Blood Samples.**
Haemoglobin concentrations were measured by the haematology laboratory of the Royal Infirmary of Edinburgh. Human chorionic gonadotrophin concentrations were assayed with commercial reagents (Serono) by the Reproductive Endocrinology Laboratory in the Centre for Reproductive Biology, Edinburgh. The lower limit of sensitivity of the assay was 3mU/ml.

**Statistics.**
The mean ± standard error is shown for normally distributed data. The median (range) of data not normally distributed is shown. Categorical data were analysed using the Chi square test. T-test for paired and independent samples was used for comparison of normally distributed data. The Mann Whitney U test was used for non-parametric comparison of data which were not normally distributed. The Statworks and Statview 512 programmes for Apple Macintosh computer were used for calculation.

**Results.**
The characteristics of the women recruited to the three groups are shown in Table 2.1. There were no significant differences between the three groups. The outcome of treatment of the three groups is shown in Table 2.2.
### Table 2.1: Patient Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg)</th>
<th>Mifepristone (mg)</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Parous (%)</th>
<th>Gestation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=20</td>
<td>600</td>
<td>27.2 ± 1.2</td>
<td>25.2 ± 1.0</td>
<td>166.4 ± 1.3</td>
<td>60.8 ± 2.6</td>
<td>9 (30)</td>
<td>49.1 ± 0.9</td>
</tr>
<tr>
<td>n=30</td>
<td>400</td>
<td>26.6 ± 1.1</td>
<td>26.9 ± 1.5</td>
<td>164.0 ± 1.0</td>
<td>59.8 ± 1.6</td>
<td>14 (47)</td>
<td>47.9 ± 0.8</td>
</tr>
<tr>
<td>n=30</td>
<td>300</td>
<td>25.2 ± 1.0</td>
<td>24.9 ± 0.9</td>
<td>163.8 ± 1.0</td>
<td>61.0 ± 2.6</td>
<td>10 (50)</td>
<td>48.8 ± 0.8</td>
</tr>
</tbody>
</table>

Data show mean ± standard error. "n" shows number (%).
<table>
<thead>
<tr>
<th>GROUP</th>
<th>DOSE OF COMPLETE ABORTION</th>
<th>DOSE OF INCOMPLETE ABORTION</th>
<th>(%) COMPLETE</th>
<th>(%) INCOMPLETE</th>
<th>(mg)</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500</td>
<td></td>
<td>20 (100)</td>
<td>0 (0)</td>
<td>1</td>
<td>30</td>
<td>27</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
<td></td>
<td>27 (90)</td>
<td>3 (10)</td>
<td>0</td>
<td>30</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td></td>
<td>60 (100)</td>
<td>10 (0)</td>
<td>0</td>
<td>30</td>
<td>90</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ALL n = 80

Table 2.2

Treatment Outcome (Dose of Mifepristone).
Seventy six (95%) of the 80 women aborted completely. There were no continuing pregnancies and only four (5%) women required surgical evacuation of uterus. There was no significant difference between the three groups in terms of complete abortion rates. Of the 24 women in Group 1, 30 in Group 2 and 20 in Group 3 who received an initial half pessary, only 3, 6 and 1 respectively required the remaining half pessary (not significant, \( p = 0.31 \)). Treatment outcome did not differ significantly between the three prostaglandin dose regimes (Table 2.3).

Of the four women requiring surgical evacuation of the uterus, one woman in Group 1 of 50 days amenorrhoea underwent emergency haemostatic curettage five hours following the insertion of half of a 1 mg gemeprost pessary. Under anaesthesia the products of conception were removed from the cervical os with a subsequent rapid reduction in blood loss. She was not clinically shocked and did not require blood transfusion. Three women in Group 2 required surgical evacuation. One woman of 53 days gestation at the start of treatment had persistent vaginal spotting for five weeks. Although her serum hCG level had fallen appropriately (from 31,000 mU/l at recruitment to 195 mU/ml at four week review), an ultrasound scan was suggestive of minimal retained products of conception. Curettage yielded minimal amounts of tissue which were histologically shown to comprise of necrotic trophoblast only.

The second woman in Group 2 to undergo surgical evacuation was 50 days from her last period at the start of treatment. After an initial fall in her hCG level (from 29,190 mU/ml at recruitment to 3,672 mU/ml seven days after treatment), her levels of hCG plateaued (4,273 mU/ml) two weeks following treatment and a small, though well defined area of retained products of conception was identified on ultrasound scan. Curettage performed 17 days following treatment, produced necrotic trophoblast with no fetal parts. The third woman in Group 2 requiring curettage was 48 days gestation when treated. Her serum hCG level at recruitment was 37,890 mU/ml and fell to 2,413 mU/ml over the week following treatment. This level plateaued at the second follow up visit (1,856 mU/ml) and rose by four weeks to 6,180 mU/ml. Ultrasound scan indicated minimal uterine debris and curettage performed 30 days following treatment yielded necrotic trophoblast but no fetal parts.

Table 2.4 shows the interval to bleeding and pain following mifepristone.
<table>
<thead>
<tr>
<th>Treatment Outcome (dose of gemeprost pessary)</th>
<th>Whole 1 mg Pessary</th>
<th>Half 1 mg Pessary x 2</th>
<th>Half 1 mg Pessary x 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>3 (5%)</td>
<td>6 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>61 (95%)</td>
<td>10  (90%)</td>
<td>64  (100%)</td>
</tr>
</tbody>
</table>

Table 2.3
<table>
<thead>
<tr>
<th>Group</th>
<th>Bleeding Onset (hours after mifepristone)</th>
<th>Pain Onset (hours after mifepristone)</th>
<th>Products of Conception Identified (%)</th>
<th>Interval to Abortion (hours after gemeprost)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.2 (2.3, 9.2)</td>
<td>45.6 (21.8, 52.6)</td>
<td>15</td>
<td>4.2 (2.5, 7.3)</td>
</tr>
<tr>
<td></td>
<td>500 mg mifepristone</td>
<td>500 mg mifepristone</td>
<td>600 mg mifepristone</td>
<td>400 mg mifepristone</td>
</tr>
<tr>
<td>2</td>
<td>4.4 (2.3, 9.2)</td>
<td>35.0 (19.5, 56.2)</td>
<td>23</td>
<td>4.4 (2.3, 7.3)</td>
</tr>
<tr>
<td></td>
<td>600 mg mifepristone</td>
<td>400 mg mifepristone</td>
<td>35.0 (19.5, 56.2)</td>
<td>600 mg mifepristone</td>
</tr>
<tr>
<td>3</td>
<td>4.2 (2.6, 6.4)</td>
<td>40.5 (20.9, 52.1)</td>
<td>23 (77)</td>
<td>4.2 (2.5, 7.3)</td>
</tr>
<tr>
<td></td>
<td>33.5 (21.5, 58.2)</td>
<td>45.6 (21.5, 52.1)</td>
<td>23</td>
<td>33.5 (21.5, 58.2)</td>
</tr>
</tbody>
</table>

Data show median (range) or number (%).
Bleeding was induced in all 80 women and there was no significant difference in the median onset of bleeding between the three groups. Overall, bleeding commenced 36 hours after mifepristone ingestion, prior to prostaglandin. The median onset of pain was 46.7 hours after mifepristone overall and individually there was no significant difference in this time interval between the three groups.

Products of conception were identified following prostaglandin administration during the treatment of 65% of women 4.2 hours after gemeprost. There were no significant differences between the three groups either in the percentage of women in whom products were identified or in the interval to abortion. (Table 2.4).

The incidence of nausea, vomiting and diarrhoea did not increase significantly in any of the groups individually during treatment. However, when data were pooled there was a small though significant increase in the incidence of vomiting (p <0.01) and diarrhoea (p <0.05) on Day 3 following gemeprost administration compared with pretreatment and Days 1 and 2 (Table 2.5). The incidence of gastro-intestinal side-effects did not differ between the three different doses of gemeprost (whole 1 mg pessary, two half pessaries, one half pessary).

None of the women required analgesia during the 48 hours following mifepristone. Table 2.6a shows analgesic used following prostaglandin administration.

There was no significant difference between the three groups in the use of no analgesia, oral analgesia or intramuscular diamorphine. However, when oral analgesia was subdivided into paracetamol use and dihydrocodeine use, Group 1 was found to use significantly more dihydrocodeine than Groups 2 or 3. Further analysis revealed that within Group 1 the use of dihydrocodeine or other analgesia did not differ between women receiving a half or a whole 1 mg pessary (Table 2.6b). The use of intramuscular diamorphine was low in all groups with only six (8%) of all women requiring parenteral opiate analgesia. Overall bleeding continued for 12 days after treatment with a large range in results (Table 2.7).
<table>
<thead>
<tr>
<th>GROUP</th>
<th>500 mg mifepristone</th>
<th>400 mg mifepristone</th>
<th>600 mg mifepristone</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>GROUP 3</td>
<td>3</td>
<td>8</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2.5: Gastrointestinal side effects during treatment with mifepristone and gemeprost.
Table 2.6a. DOSE OF MIFEPRISTONE GROUP (mg)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mifepristone</th>
<th>Diamorphine</th>
<th>Paracetamol</th>
<th>Dihydrocodeine</th>
<th>Analgesic Use in All Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>300</td>
<td>16 (6)</td>
<td>12 (46)</td>
<td>37 (46)</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
<td>300</td>
<td>16 (6)</td>
<td>12 (46)</td>
<td>37 (46)</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>300</td>
<td>16 (6)</td>
<td>12 (46)</td>
<td>37 (46)</td>
</tr>
</tbody>
</table>

* p < 0.01
<table>
<thead>
<tr>
<th>Group</th>
<th>Mifepristone</th>
<th>Gemeprost Pessary</th>
<th>Analgesia Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td>9 (30)</td>
<td>7 (29)</td>
<td>NIL</td>
</tr>
<tr>
<td>Half</td>
<td>6 (20)</td>
<td>4 (67)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>NIL</td>
<td>14 (47)</td>
<td>10 (42)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 2.6b

Analgesia use in Group I.
Table 2.7 Duration of bleeding following treatment, interval to next menses, and haemoglobin concentration before and after treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration of bleeding (days)</th>
<th>Interval to next menstrual period (days)</th>
<th>Haemoglobin (g/dl) before treatment</th>
<th>Haemoglobin (g/dl) 7 days after abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 (4, 35)</td>
<td>31.5 ± 2.0</td>
<td>12.8 ± 0.2</td>
<td>12.7 ± 0.2</td>
</tr>
<tr>
<td>2</td>
<td>12 (4, 35)</td>
<td>30.8 ± 1.2</td>
<td>13.1 ± 0.1</td>
<td>12.8 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>12.5 ± 0.9</td>
<td>30.0 ± 1.7</td>
<td>13.5 ± 0.1</td>
<td>13.1 ± 0.2</td>
</tr>
</tbody>
</table>

Data show median (range) or mean ± standard error.

* p < 0.01
+ p < 0.05
There was no significant difference between the three groups in the duration of bleeding following treatment or in the interval to the next menstrual period which occurred around 31 days following treatment when all groups were considered. Data were unavailable or not considered for calculation of the interval to the next period in seven women; four women who underwent curettage and three women who did not provide this information after their 4 week follow up visit. The haemoglobin concentration fell significantly following treatment in all groups.

The serum concentration of hCG fell dramatically during the week following treatment (Table 2.8).

hCG was still detectable two and four weeks following treatment in all groups. There was no significant difference between the three groups in hCG levels at recruitment or follow up visits.

None of the women developed pelvic infection requiring hospital admission following treatment. Seven women received antibiotic therapy. Endocervical swabs performed because of offensive vaginal loss rather than pain or pyrexia, yielded a variety of pathogenic organisms on culture including trichomonas vaginalis, bacteroides, gonococcus.
Table 2.8

Table 2.8

<table>
<thead>
<tr>
<th>Recruitmen</th>
<th>7 days after</th>
<th>14 days after</th>
<th>28 days after</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 mg mifepristone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35865 (13, 12160)</td>
<td>35.9 (2.4990)</td>
<td>444 (6, 2438)</td>
<td>444 (3, 4937)</td>
</tr>
<tr>
<td>GROUP 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg mifepristone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38380 (370, 2432)</td>
<td>43.7 (4.5)</td>
<td>43.7 (4.5)</td>
<td>43.7 (4.5)</td>
</tr>
<tr>
<td>GROUP 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg mifepristone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50000 (282, 10110)</td>
<td>500 (2.438)</td>
<td>500 (2.438)</td>
<td>500 (2.438)</td>
</tr>
</tbody>
</table>

Data show median (range).

Significantly lower than preceding value p < 0.0001

* ALT
**Discussion.**

Complete abortion was induced in 95% of women in this study using a single dose of mifepristone in combination with an otherwise subtherapeutic dose of gemeprost. This not only confirms the findings of smaller studies but demonstrates that simplification of the drug regime does not compromise abortion rates or increase side effects. The abortion rate in this study compares well with that of Bygdeman and Swahn (1985) and Cameron et al (1986) and has the advantage of being achieved with considerably less hospital contact for participating women.

The dose of mifepristone used in this study did not appear to affect outcome with the abortion rate not differing significantly between women receiving 400 mg, 500 mg, or 600 mg. This is in keeping with the findings of studies of plasma levels (Heikinheimo et al, 1987b; Swahn et al, 1986) and uterine activity (Swahn & Bygdeman, 1988) following various doses of mifepristone which demonstrate no correlation between the initial doses of mifepristone and subsequent plasma level or effect.

The open study design and small numbers prevent formal determination of small differences in treatment outcome in this study. However, this point has been addressed subsequently by both single and multicentre trials. A multicentre trial involving 385 women of up to 49 days amenorrhoea, randomly treated woman with either mifepristone 25 mg five times at 12 hourly intervals or mifepristone 600 mg as a single oral dose, followed by gemeprost 1 mg pessary. Treatment outcome was identical in both groups with an overall abortion rate of 92.7% (WHO, 1991). Norman et al, found no difference in efficacy between 200 mg, 400 mg and 600 mg of mifepristone used in combination with gemeprost 1 mg with 98% of women of less than 56 days amenorrhoea, aborting (Norman et al, 1992). In a larger multicentre trial involving 1,182 women of less than 56 days the World Health Organization found no difference in outcome when 200 mg, 400 mg and 600 mg of mifepristone was given prior to gemeprost 1 mg (WHO, 1993).

When mifepristone is used alone to induce abortion before 56 days of amenorrhoea, there is a low incidence of side effects but unacceptably high incidence of incomplete abortion and continuing pregnancy (Chapter 1). By adding a small dose of prostaglandin to treatment with mifepristone, complete abortion was induced in 95% of women in this study without a large increase in the incidence of side effects. In none of the groups did the incidence of vomiting or diarrhoea increase significantly during treatment. Overall, 29% of women vomited on Day 3 following prostaglandin and 9% experienced diarrhoea. This compares well with 50% incidence of...
gastrointestinal side effects found when prostaglandin analogues alone are used to induce early abortion (Bygdeman et al, 1983), and is similar to the rates reported by the UK Multicentre Trial of 600 mg mifepristone and gemeprost 1 mg (UK Multicentre Trial, 1990) and the WHO Multicentre Trial of 200 mg, 400 mg and 600 mg of mifepristone and gemeprost 1 mg (WHO 1993).

The comparatively low incidence of prostaglandin-related vomiting and diarrhoea is not unexpected when the dose of gemeprost used in this study is considered. In studies of the use of gemeprost alone to induce early abortion, the majority of women require five 1 mg pessaries to achieve complete abortion (Smith & Baird, 1980; WHO, 1982; Cameron & Baird, 1988). In this study, only one 1 mg pessary or less was required to induce complete abortion following mifepristone.

The use of intramuscular diamorphine and by inference the incidence of severe pain, was small in this study with only six women (8%) needing parenteral opiate for analgesia. This is very similar to the 9% of women requiring intramuscular opiate reported by Bygdeman and Swahn following mifepristone and sulprostone (Bygdeman & Swahn, 1985) but less than that reported by the WHO (11-14.5%) (WHO, 1993) and the UK Multicentre Trial (28%) (UK Multicentre Trial, 1990). The opiate use in this study was considerably less than the reported use of opiates following the use of gemeprost alone. In one multicentre study of gemeprost as an early abortifacient, over 70% of women required intramuscular opiate in some centres (WHO, 1982a).

There were no serious complications during the treatment of any of the women. One woman required haemostatic curettage shortly following prostaglandin administration. In this case blood loss was reduced simply by removing products of conception from the cervical os and the woman was neither shocked nor in need of blood transfusion and in retrospect, could have been managed without surgical intervention. In larger, subsequent trials of mifepristone in combination with gemeprost or sulprostone, the reported rate of haemostatic curettage is similar: 0.4 - 0.8% in a large French Multicentre Trial (Ulmann et al, 1992) and 1% in the UK Multicentre Trial (UK Multicentre Trial, 1990). Haemoglobin concentration fell significantly following treatment in all groups. Again, this finding has been replicated in a series of subsequent studies (WHO, 1993; UK Multicentre Trial, 1990; Henshaw et al, 1994; Thonneau et al, 1995). Although the fall was small and would not be expected to have a negative impact on a well nourished population, it remains to be determined what the health effects of such a fall would be on an endemically iron deficient population.
The duration of bleeding following treatment was comparable with that following medical abortion with other agents and vacuum aspiration (Chapter 1). There was, however, a large range in the results and some women continued to bleed until the onset of their next period. Early in the study this led to surgical evacuation of the uterus in one woman but as the study progressed, the threshold for intervention in such cases was raised. Mandelin has attributed prolonged bleeding and a slow decline in hCG levels to the presence of small amounts of residual trophoblast (Mandelin, 1978) and in this study hCG was detectable in serum of some women two and four weeks following treatment. It seems likely that this is due to both small amounts of residual trophoblast and the long half life of hCG.

This study has shown that medical abortion with a single dose of mifepristone and an otherwise subtherapeutic dose of prostaglandin compares well with vacuum aspiration in terms of efficacy and acceptability. The abortion rate in this study was as high as that achieved surgically at the same gestation and there were no serious complications. A serious complication rate of 2% can be anticipated when vacuum aspiration is used to terminate pregnancy (Franks, 1985) and the incidence of complications and failure of the procedure is increased before seven weeks gestation (Tietze & Lewit, 1972). The low incidence of side effects, in particular severe pain, suggests that this method of medical abortion will have wide application.

In summary, a single dose of mifepristone in combination with a small dose of gemeprost is as effective as serial administration of the antigestagen followed by prostaglandin for the induction of early abortion. The high abortion rate and low incidence of side effects and complications suggest that this combination of mifepristone and prostaglandin analogue provides a viable alternative to vacuum aspiration.
CHAPTER 3.

INDUCTION OF EARLY ABORTION WITH 600 mg OF MIFEPRISTONE AND TWO DIFFERENT DOSES OF GEMEPROST PESSARY.
Introduction.

While efficacy of a given method of medical termination of early pregnancy is important, it is not the only determinant of usefulness of that method. Acceptability of the method to women treated must also be considered. Rosen et al have shown that acceptability is closely related to the incidence of side effects caused by an abortifacient, with women finding medical abortion unacceptable when they experience a high incidence of side effects, in particular pain (Rosen et al, 1979; 1984).

Mifepristone causes few side effects but when used alone is not an effective abortifacient. Combination of treatment with mifepristone with prostaglandin provides an effective method of medical abortion (Chapter 2; Bygdeman & Swahn, 1985; Cameron et al, 1986) and the dose of mifepristone used appears to have little bearing on either the treatment outcome or the incidence of side effects (Chapter 2). It would seem likely that it is the amount of prostaglandin used that determines the incidence of gastro-intestinal side effects and pain when mifepristone and prostaglandin are used to induce abortion.

In this Chapter the efficacy and side effects of treatment with 600 mg of mifepristone in combination with two different doses of gemeprost are studied during the induction of early abortion in 120 women.

Methods.

One hundred and twenty women of 56 days amenorrhoea were recruited following referral by local family planning services or general practitioners, in the same manner as those in Chapter 2. The inclusion and exclusion criteria for the study were the same as those described in Chapter 2. Local Ethical Committee approval was granted for the study. All women had grounds for abortion under the provision of the 1967 Abortion Act and written informed consent was obtained from each woman prior to participation in the study.

Recruitment.

A full history was taken and examination performed, including pelvic examination. Pregnancy was confirmed by measurement of the serum level of human chorionic gonadotrophin and gestational age assessed by an accurate menstrual history and pelvic ultrasound scan. Blood was taken for grouping and assessment of haemoglobin and hCG levels. Arrangements were made for admission (usually within two days) and all women were asked to keep a daily record of the incidence of
nausea, vomiting, diarrhoea and any other symptoms, to be commenced on the day prior to treatment.

**Treatment.**

**Day 1: Mifepristone.**

On the first day of treatment all women were admitted to hospital and received a single oral dose of 600 mg mifepristone. No dietary restrictions were imposed. Hourly recordings of temperature, blood pressure and pulse rate were commenced just prior to mifepristone ingestion and continued for four hours. Women were questioned hourly as to the incidence of nausea, vomiting, diarrhoea or other symptoms. Women were then discharged home. In addition to keeping a daily record of symptoms experienced, women were asked to note the time of onset of vaginal bleeding and/or pelvic pain.

**Day 3: Gemeprost.**

Forty eight hours following mifepristone administration all women were re-admitted to hospital to commence treatment with prostaglandin. The first 30 women recruited to the study received one half of a 1 mg gemeprost vaginal pessary (halved with a scalpel) which was inserted into the posterior fornix of the vagina. The next 30 women recruited received a whole 1 mg gemeprost vaginal pessary. The remaining 60 women were recruited to a double blind randomised trial of a half or a whole 1 mg gemeprost pessary. The prostaglandin was administered to these women by a member of staff who was not involved in the study and who played no subsequent part in patient management. In this way, neither the patient nor the investigator knew the dose of gemeprost given.

All women remained supine for one hour following prostaglandin administration. No dietary restrictions were imposed. Hourly measurement of temperature, blood pressure and pulse rate was commenced prior to gemeprost insertion and continued for four hours after. Women continued to keep a record of symptoms experience and, in addition, were questioned hourly during the observation period about the incidence of nausea, vomiting, diarrhoea or other symptoms.

Prophylactic medications were not prescribed, however, and analgesia was given as required. Oral paracetamol (1G) was given for mild pain, oral dihydrocodeine (30 mg) was given for moderate pain and intramuscular diamorphine (5 mg) was given for severe pain.
Women were discharged home at least four hours after prostaglandin administration once vaginal bleeding and pelvic pain had settled. A speculum examination was performed prior to discharge to ensure that products of conception were not present at the cervical os.

**Follow Up Appointments.**
Women were reviewed 7, 14 and 28 days following treatment and discharged from care after the onset of their next menstrual period. Non-hormonal methods of contraception (excluding the IUCD) were used until normal menstruation had been established. At each visit a history of any problems or medical intervention was taken. The daily symptom record was reviewed. A vaginal examination was performed to assess the state of the cervix and uterine size. Blood was taken for estimation of haemoglobin level at the first visit and for estimation of the level of hCG at every visit. Abortion was considered complete if by the final visit the cervix was closed, the uterus normal in size, vaginal bleeding had ceased and serum level of hCG was less than 400 mU/ml. Six women in whom incomplete abortion was suspected underwent a pelvic ultrasound scan to confirm the diagnosis.

**Blood Samples.**
Haemoglobin concentration was measured by the Haematology Laboratory of the Royal Infirmary of Edinburgh. hCG was assayed using commercial reagents (Serono) by the Reproductive Endocrine Laboratory, Centre for Reproductive Biology, Edinburgh. The lower limit of sensitivity of the assay was 3mU/ml serum.

**Statistical Methods.**
Normally distributed data are presented as mean ± standard error of the mean. Data which were not normally distributed are presented as median (range). Categorical data were analysed by the Chi square test. The Mann Whitney U test was used for comparison of data which were not normally distributed, the t-test for independent samples and t-test for paired samples were used for comparison of normally distributed data. The Statworks and Statview 512 computer programmes for Apple Macintosh computer were used for calculation throughout.

**Results.**
Table 3.1 shows the characteristics of the women treated. There were no significant differences between the four groups of women in terms of personal characteristics. Table 3.2 shows the outcome of treatment.
<table>
<thead>
<tr>
<th></th>
<th>NON-RANDOMISED</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient</td>
<td>Characteristic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>Height (cm)</td>
<td>Weight (kg)</td>
<td>Gestation (days)</td>
<td>Parous (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half Pessary</td>
<td>47.4 ± 1.1</td>
<td>165.5 ± 1.2</td>
<td>61.5 ± 1.2</td>
<td>48.8 ± 0.6</td>
<td>13 (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Pessary</td>
<td>59.0 ± 1.2</td>
<td>164.7 ± 1.0</td>
<td>60.0 ± 1.6</td>
<td>48.7 ± 1.2</td>
<td>8 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>164.0 ± 0.9</td>
<td>164.2 ± 1.0</td>
<td>59.0 ± 1.2</td>
<td>46.9 ± 1.0</td>
<td>10 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.2 ± 1.1</td>
<td>26.5 ± 1.2</td>
<td>27.1 ± 1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data show mean ± standard error, save for parity which is presented as number of parous women (%).
Table 3.2

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Non Randomised</th>
<th>Randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Abortion</td>
<td>30 (100%)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Incomplete Abortion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Continuing Pregnancy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Data show number of women (%)

- One woman aborted 36 hours after mifepristone administration before gemeprost administration.
- Haemostatic curettage 8 hours after gemeprost administration.

Note: 8 hours after gemeprost administration, 1 woman aborted 36 hours after mifepristone administration, prior to gemeprost.
One hundred and nineteen of the 120 women recruited to the study aborted completely, requiring no surgical intervention. There were no continuing pregnancies. Only one woman, randomised to receive a half pessary, underwent surgical evacuation of the uterus. This woman, a primigravida 53 days from her last period at the start of treatment, required haemostatic curettage eight hours following the administration of half of a 1 mg gemeprost pessary. An attempt to reduce the amount of vaginal blood loss by further prostaglandin administration failed and she was taken to theatre. Under anaesthesia the gestational sac was found to have incompletely separated and surgical evacuation of the uterus was performed. Her haemoglobin concentration fell from 11.5 g/dl to 8.5 g/dl and she was given a two unit transfusion of red cell concentrate in treatment of symptomatic anaemia.

There were no significant differences between the four groups in terms of treatment outcome. One woman randomised to receive a whole 1 mg pessary aborted prior to prostaglandin administration, 36 hours after mifepristone ingestion. She was, therefore, excluded from the analysis of side effects subsequent to prostaglandin.

Bleeding was induced in all women. Table 3.3 details bleeding patterns. The median time interval to onset of bleeding following mifepristone did not significantly vary between the four groups with bleeding commonly starting prior to prostaglandin in all groups. Bleeding continued for 14.5, 14.5, 13 and 12 days in the non-randomised half and whole pessary groups and randomised half and whole pessary groups respectively. There was a large range in the duration of bleeding with some women continuing to spot vaginally until the onset of their next period. The groups did not differ in their length of bleeding and the median interval to the next period was similar in all four groups. (Table 3.3).

Haemoglobin levels fell following treatment in all groups but this was only statistically significant in women receiving a whole 1 mg pessary in the randomised group (p <0.05). The change in the level of haemoglobin was similar in all four groups: -0.3 g/dl to -0.4 g/dl. Only one woman required blood transfusion as discussed above. (Table 3.4).
Table 3.3

<table>
<thead>
<tr>
<th></th>
<th>NON RANDOMISED</th>
<th>RANDOMISED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mifepristone (hours)</td>
<td>34</td>
<td>32 (23.8, 51.2)</td>
</tr>
<tr>
<td>Whole pessary (n=30)</td>
<td>32</td>
<td>32 (24.8, 53.7)</td>
</tr>
<tr>
<td>Half pessary (n=30)</td>
<td>33 (23.8, 41.2)</td>
<td>33 (24.8, 53.7)</td>
</tr>
<tr>
<td><strong>Duration of bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(days)</td>
<td>14.5 (4, 29)</td>
<td>13 (3, 35)</td>
</tr>
<tr>
<td></td>
<td>12 (5, 44)</td>
<td></td>
</tr>
<tr>
<td><strong>Interval to next menstrual period (days)</strong></td>
<td>33 (24, 49)</td>
<td>32 (23, 56)</td>
</tr>
<tr>
<td></td>
<td>33 (23, 41)</td>
<td>34 (25, 60)</td>
</tr>
</tbody>
</table>

Data show median (range).
<table>
<thead>
<tr>
<th></th>
<th>Half Pessary (n=30)</th>
<th>Whole Pessary (n=30)</th>
<th>NON RANDOMISED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>13.0 ± 0.2</td>
<td>13.0 ± 0.2</td>
<td>12.5 ± 0.2</td>
</tr>
<tr>
<td>Haemoglobin (g/dl) 7 days after recruitment</td>
<td>12.4 ± 0.2*</td>
<td>12.6 ± 0.2*</td>
<td>12.7 ± 0.2</td>
</tr>
<tr>
<td>Haemoglobin (g/dl) Recruitment</td>
<td>13.0 ± 0.2</td>
<td>13.0 ± 0.2</td>
<td>12.4 ± 0.2</td>
</tr>
</tbody>
</table>

Change in haemoglobin

**Table 3.4**

Data show mean ± standard error

*Significantly less than recruitment value p > 0.05

Data show mean ± standard error

*Significantly less than recruitment

\[ \text{(g/dl)} \]

7 days after recruitment

Haemoglobin (g/dl)

Recruitment

Haemoglobin (g/dl)

Randomised

Non Randomised

Haemoglobin levels before and after treatment: change in haemoglobin.
Thirty (100%) women in the non randomised group receiving a half pessary, 28 (93%) in the non randomised group receiving a whole pessary, 29 (97%) randomised to receive a half pessary and 28 (93%) randomised to receive a whole pessary, experienced pelvic discomfort during treatment. Of these women, the median time of onset of pain following mifepristone did not differ significantly between the four groups and commonly occurred prior to prostaglandin administration (Table 3.5). Only one woman required analgesia during the first 48 hours of treatment, taking 1G of oral paracetamol for mild dysmenorrhoeic-like discomfort. (Table 3.6).

Significantly more women in the non-randomised group receiving a half pessary required no analgesia with 67% of this group using no analgesics (p <0.005). The pattern of intramuscular opiate use was similar in the randomised and non randomised groups with a higher percentage of women receiving the larger dose of prostaglandin requiring diamorphine in treatment of severe pain. In the non-randomised group, only two (7%) of women required diamorphine following administration of a half pessary compared with seven (23%) women who had received a whole pessary. This increased use of intramuscular opiate was statistically significant in the randomised group receiving a whole pessary with 10 (34%) women using diamorphine (p <0.05). Only four (13%) women randomised to receive a half pessary required diamorphine. The use of paracetamol and dihydrocodeine for mild to moderate pain was similar in all four groups (Table 3.7). Although parous women used proportionately less diamorphine than primiparous women, this did not achieve statistical significance in any group (Table 3.8).

The incidence of nausea was high in all groups prior to treatment (Day 0) and the trend was a decrease in incidence during treatment. This was only of statistical significance in the group randomised to receive a half pessary (p <0.05). The reported incidence of vomiting and diarrhoea did not increase significantly in any group during treatment and there were no significant differences in the incidence of these symptoms between the four groups. Figure 3.1 illustrates the incidence of nausea, vomiting and diarrhoea in the four groups before and during treatment.
<table>
<thead>
<tr>
<th>Group</th>
<th>Median (Range) after mifepristone (hrs)</th>
<th>Onset of pain (hrs)</th>
<th>Onset of pain following mifepristone (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half Pessary</td>
<td>3.1, 5</td>
<td>29.3</td>
<td>13.3, 52.1</td>
</tr>
<tr>
<td>Non Randomised</td>
<td>3.1, 1.5</td>
<td>34.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Whole Pessary</td>
<td>5.5, 52.6</td>
<td>28</td>
<td>5.5, 51.2</td>
</tr>
</tbody>
</table>

Data show median (range).
<table>
<thead>
<tr>
<th>Analgesia</th>
<th>Half Pessary Randomised</th>
<th>Whole Pessary Randomised</th>
<th>Half Pessary Non Randomised</th>
<th>Whole Pessary Non Randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamorphine</td>
<td>34%</td>
<td>13%</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>7%</td>
<td>13%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>38%</td>
<td>47%</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Nil</td>
<td>21%</td>
<td>27%</td>
<td>43%</td>
<td>63%+</td>
</tr>
</tbody>
</table>

Data show percentage of women.

\[ \chi^2 = 13.747, p > 0.005 \]
\[ \chi^2 = 8.356, p < 0.05 \]

\(\chi^2 = 8.356, p < 0.05\)
### Table 3.7

<table>
<thead>
<tr>
<th></th>
<th>Non-Randomised</th>
<th>Randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>% parous women using diamorphine</td>
<td>0%</td>
<td>39%</td>
</tr>
<tr>
<td>% primiparous women using diamorphine</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>% primiparous women using diamorphine</td>
<td>0%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Data show percentage of women.
Table 3.8: Incidence of gastrointestinal side effects before and during treatment.

<table>
<thead>
<tr>
<th></th>
<th>Half Pessary</th>
<th>Whole Pessary</th>
<th>Half Pessary</th>
<th>Whole Pessary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomised</td>
<td>Non Randomised</td>
<td>Randomised</td>
<td>Non Randomised</td>
</tr>
<tr>
<td>Nausea Days 0</td>
<td>%73%</td>
<td>%70%</td>
<td>%73%</td>
<td>%73%</td>
</tr>
<tr>
<td>Nausea Days 1</td>
<td>%67%</td>
<td>%53%</td>
<td>%67%</td>
<td>%67%</td>
</tr>
<tr>
<td>Nausea Days 3</td>
<td>%57%</td>
<td>%43%</td>
<td>%57%</td>
<td>%57%</td>
</tr>
</tbody>
</table>

Data show percentage of women.

\[ x^2 = 10.179, p < 0.05 \]
The incidence of nausea, vomiting and diarrhoea in the four groups before and during treatment.
The products of conception were identified during the treatment of 23 (77%), 28 (93%), 25 (83%) and 27 (93%) women in the non-randomised half and whole pessary groups and randomised half and whole pessary groups respectively. Abortion occurred at a median of between three and four hours following prostaglandin administration and this time interval did not differ significantly between groups (Table 3.9).

The serum concentration of hCG fell precipitously following treatment but was still detectable four weeks later in all groups. None of the women treated in the study developed pelvic infection following abortion (Table 3.10).

Discussion.
This study has confirmed the efficacy of mifepristone and prostaglandin for the induction of early medical abortion. The overall complete abortion rate of 99% is similar to that achieved in Chapter 2 and the slight improvement in outcome probably reflects increased experience of the technique rather than an advantage of a larger dose of antigestagen. Similar outcome has also been reported in multicentre trials with much the same drug regime (600 mg mifepristone and 1 mg gemeprost, (UK Multicentre Trial, 1990) a three or four day course of mifepristone (total dose 150 mg to 200 mg mifepristone) and 0.25 mg sulprostone (WHO, 1989) and 600 mg mifepristone in combination with either 1 mg gemeprost or varying doses (0.25 mg, 0.375 mg, 0.5 mg) of sulprostone (Silvestre et al, 1990). Combination of mifepristone with misoprostol, another PGE1 analogue, given orally or vaginally, results in comparable abortion rates (Aubeny & Baulieu, 1991; Norman et al, 1991c; Peyron et al, 1993; El-Refaey & Templeton, 1994a;b; Penney et al, 1995).

Use of a half rather than a whole 1 mg pessary did not compromise complete abortion rates. Reduction of the dose of prostaglandin did not influence the incidence of gastro-intestinal side effects during treatment in comparison with women receiving a whole pessary. The incidence of vomiting and diarrhoea did not significantly increase with either dose regime. The incidence of severe pain did appear to be related to prostaglandin dose. Even with the small numbers of women in each group studied there was found to be a statistically significant increase in the use of intramuscular opiate amongst women randomised to receive a whole pessary and the same trend was seen in the non-randomised group.
### Table 3.9

<table>
<thead>
<tr>
<th>Identification and time of passage of products of conception.</th>
<th>Non-Randomised</th>
<th>Randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half Pessary</td>
<td>25 (83%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Whole Pessary</td>
<td>27 (93%)</td>
<td></td>
</tr>
<tr>
<td>Time interval to abortion following gemeprost (hrs).</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>(1.8, 4.8)</td>
<td>(2.0, 5.8)</td>
</tr>
<tr>
<td>n = 29</td>
<td>n = 30</td>
<td>n = 30</td>
</tr>
</tbody>
</table>
| Data show number (percentage) and median (range).
Table 3.10
Serum human chorionic gonadotrophin concentration (mU/ml)

<table>
<thead>
<tr>
<th></th>
<th>Before and after treatment</th>
<th>28 days after</th>
<th>14 days after</th>
<th>7 days after</th>
<th>Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half Pessary</td>
<td>111</td>
<td>1359</td>
<td>1359</td>
<td>1359</td>
<td></td>
</tr>
<tr>
<td>Whole Pessary</td>
<td>781</td>
<td>181</td>
<td>181</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>Randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half Pessary</td>
<td></td>
<td>471</td>
<td>471</td>
<td>471</td>
<td></td>
</tr>
<tr>
<td>Whole Pessary</td>
<td></td>
<td>781</td>
<td>781</td>
<td>781</td>
<td></td>
</tr>
<tr>
<td>Recruitement</td>
<td></td>
<td>145</td>
<td>145</td>
<td>145</td>
<td></td>
</tr>
</tbody>
</table>

Data show median (range).
The influence of dose of prostaglandin on opiate analgesic requirements and, by inference, severe pain, can be seen in trials of mifepristone and misoprostol. In studies using 400 µg to 600 µg of misoprostol there is a low reported use of opiates: from 0 to 3% (Peyron et al, 1993; Thong & Baird, 1992b). When a larger dose of misoprostol is administered after mifepristone pretreatment (800 µg orally or vaginally) 10 to 16% of women require parenteral opiate (El-Refaey & Templeton, 1994a; El-Refaey et al, 1995).

The use of diamorphine did not differ significantly between parous and primiparous patients (Table 3.7). The pattern of opiate use by women receiving 1 mg gemeprost in this study was very similar to that reported by a large multicentre study of 600 mg mifepristone and 1 mg gemeprost where 13% of parous women and 37% of primiparous women required opiate for analgesia (UK Multicentre Trial, 1990). Although no statistically significant change was demonstrated in diamorphine use in parous and primiparous women given a half or a whole pessary both groups of women required more diamorphine when given the larger dose of prostaglandin and it could be anticipated that study of larger numbers would yield statistical significance.

Pain has been shown to be a major factor in the unacceptability of methods of medical abortion (Rosen et al, 1979; 1984; Henshaw et al, 1993). While factors such as the environment in which the medical abortion is induced (Thong et al, 1992; Rosen et al, 1979; 1984), freedom of choice of abortion method and gestation at which the abortion is performed (Henshaw et al, 1993) exert an effect on both acceptability of abortion method and the incidence of pain, the dose of prostaglandin administered remains an important aetiological factor in opiate requirement during medical abortion (Grimes, 1997).

One woman in this study required haemostatic curettage and subsequent blood transfusion. The need for haemostatic curettage and blood transfusion has been reported in both single centre and multicentre studies of mifepristone and various prostaglandin analogues (Swahn & Bygdeman, 1989; Silvestre et al, 1990; UK Multicentre Trial, 1990; WHO, 1989) and a review of 10,000 women treated in France placed the incidence of heavy bleeding requiring transfusion at 0.1% (Aubeny, 1990). The risk of haemorrhage requiring transfusion as a result of vacuum aspiration is between 0.5% and 4.9% (Cates & Grimes, 1981). Although the risk of severe haemorrhage is small when mifepristone and prostaglandin are used to induce abortion, it underlines the need for medical supervision of this abortion method.
The duration of bleeding following treatment was similar to that in Chapter 2 and to other methods of medical abortion (see Chapter 1). Haemoglobin levels fell by a small amount in all groups and this has also been noted by other authors (Swahn & Bygdeman, 1989; UK Multicentre Trial, 1990). In one study this fall in haemoglobin was found to have corrected itself by 14 days following treatment (Swahn & Bygdeman, 1989).

Although medical abortion with mifepristone and prostaglandin analogue is a safe method of termination, it is not without risk. A death from myocardial infarction has been reported following the use of mifepristone and sulprostone (Lancet, 1991) and cardiac arrest has been described following the use of gemeprost pessaries (Kalra et al, 1989). It has been shown in this Chapter that a reduction of the dose of prostaglandin used by halving a 1 mg gemeprost pessary does not adversely affect successful outcome of abortion with mifepristone and it can be presumed that this reduction in prostaglandin dose reduces the risk of prostaglandin-related complications.

In summary, this study has confirmed the efficacy of treatment with a single dose of mifepristone in combination with gemeprost for the induction of early medical abortion. Use of a smaller dose of prostaglandin does not reduce the incidence of complete abortion but does reduce the incidence of severe pain. Although this combination of antigestagen and prostaglandin is a safe method of abortion, the small risk of heavy blood loss implies that medical supervision is essential. The smallest effective dose of either mifepristone or gemeprost is not yet known and requires further investigation.
CHAPTER 4.

THE EFFECTS OF PRETREATMENT WITH A PROSTAGLANDIN ANALOGUE (GEMEPROST) OR MIFEPRISTONE ON UTERINE ACTIVITY IN EARLY PREGNANCY.
Introduction.
In Chapters 2 and 3 it has been clearly demonstrated clinically that pretreatment with mifepristone increases the sensitivity of the early pregnant uterus to exogenous prostaglandins to such an extent that abortion can be induced with an otherwise non-therapeutic dose of prostaglandin analogue. This enhanced contractile response to exogenous prostaglandin can be elicited in some women as early as 24 hours, and in the majority, 36 hours following mifepristone ingestion and has been attributed, at least in part, to an increased production of endogenous prostaglandin as a result of progesterone withdrawal (Swahn & Bygdeman, 1988; Bygdeman & Swahn, 1985). Csapo and Pulkkinen have suggested that a similar mechanism exists in early pregnancy following administration of prostaglandin alone. They have suggested that prostaglandin-mediated damage to the conceptus leads to a decrease in progesterone and a consequent increase in endogenous prostaglandin production (Csapo & Pulkkinen, 1979). Although many studies have investigated uterine activity following prostaglandin administration in early pregnancy, they have concentrated on the immediate effects of stimulation and have not reported the long-term effect of the "prostaglandin impact" on uterine activity. In this Chapter the effects of pretreatment with prostaglandin on uterine activity following prostaglandin administered 48 hours later are studied in order to determine whether an initial prostaglandin impact sensitises the early pregnant uterus to exogenous prostaglandin. Comparison is made with both the effects of no pretreatment and also mifepristone pretreatment 48 hours prior to prostaglandin administration on uterine activity, in order to further investigate the mechanism of early abortion with prostaglandin alone or following mifepristone.

Methods.
Fifteen women were recruited for this study. They fulfilled the recruitment criteria described in Chapter 2. All women were less than 56 days from their last menstrual period and gestation was confirmed by an ultrasound scan. A full history was taken, examination was performed and blood was taken for estimation of the level of haemoglobin, blood group typing and measurement of serum human chorionic gonadotrophin level. The study protocol had been previously approved by the local Ethical Committee of Lothian Health Board and written, informed consent was obtained from each woman prior to participation in the study. Women were recruited into one of three treatment groups.
Group 1.
In order to investigate whether insertion of an uterine catheter had an effect on the pattern of uterine activity, five women were recruited to this control group. On the morning of the first study day women were admitted to hospital and an intrauterine pressure transducer was inserted into the uterus through the cervix (details are given under "intrauterine pressure recordings"). Uterine pressure was then recorded for three and a half hours. The pressure transducer was removed and the women discharged home. Women were re-admitted to hospital on the morning of Day 3, 48 hours following their first admission. The intrauterine pressure transducer was reinserted and following a baseline recording period of 30 minutes a 1 mg gemeprost vaginal pessary was inserted into the posterior fornix of the vagina. Recording of intrauterine pressure continued for three hours following prostaglandin administration. The pressure transducer was then removed. Women requiring anti-D prophylaxis were given this prior to discharge. All women were reviewed seven days following discharge from hospital. An ultrasound scan was performed and if abortion had not occurred, women underwent surgical evacuation of the uterus.

Group 2.
Five women were recruited to this group to determine the effect of pretreatment with a gemeprost pessary on uterine activity subsequent to a further gemeprost pessary. Following admission to hospital on the first day of the study, an intrauterine pressure transducer was inserted. A 30 minute baseline recording was made of intrauterine pressure prior to the insertion of a 1 mg gemeprost vaginal pessary into the posterior fornix of the vagina. Recording continued for a further three hours after which time the pressure transducer was removed. Women were then discharged home. They were re-admitted 48 hours following the start of treatment, on the morning of the third study day. The procedures of Day 1 were repeated with 1 mg gemeprost pessary being given 30 minutes following insertion of the pressure transducer. Women were discharged home following completion of the three hour post-prostaglandin recording period. All women were reviewed seven days following discharge. An ultrasound scan was performed and if abortion had not occurred, women underwent surgical evacuation of the uterus.

Group 3.
Five women were recruited to this group to confirm the clinical observation that pretreatment with mifepristone sensitises the uterus to exogenous prostaglandin. On Day 1 of the study women were admitted to hospital and an intrauterine pressure transducer was sited. Following a 30 minute recording period, 600 mg of mifepristone was given orally and intrauterine pressure was recorded for a further
three hours. The transducer was then removed and women discharged. The women were re-admitted on the morning of Day 3. The pressure transducer was inserted and recording conducted for 30 minutes prior to the insertion of a 1 mg gemeprost vaginal pessary, 48 hours following ingestion of mifepristone. Recording continued for three hours before removal of the pressure transducer. The subsequent management and follow-up arrangements have been described in Chapter 2.

**Intrauterine Pressure Recordings.**

**Equipment.**

Intrauterine pressure was measured by a flexible catheter tipped with a pressure transducer. This was manufactured by Gaeltec Limited (Dunvegan, Isle of Skye) and had a pressure range of between 0 and 300 mmHg. The pressure transducer was connected to an amplifier and then to a pen recorder.

**Insertion of pressure transducer.**

The procedure was carried out under sterile conditions. A vaginal speculum was passed and the cervix visualised. The pressure catheter, previously sterilised by steepage in Cidex (2% glutaraldehyde solution) for 10 minutes, was inserted in the cervical os with the aid of sponge-holding forceps and passed through the cervix into the extra-amniotic space of the uterine cavity. When fundally sited (judged by resistance to further insertion) the catheter was withdrawn by 1 to 2 cms and was, therefore, lying free in the upper part of the uterine cavity. The catheter was secured in the vagina by a tampon and taped to the woman's inner thigh. The extra-uterine end was connected to an amplifier which was, in turn, connected to a pen recorder.

**Calibration of the pressure transducer and amplifier.**

Calibration was performed prior to each recording. The system was zeroed in atmospheric pressure, a pressure of 0 being recorded on the amplifier and pen recorder when the pressure catheter was in air. The catheter was then placed in a 43 cm column of water with the pressure tip lying at the bottom thus providing a known pressure of 31.6 mmHg. The system was then adjusted so that a pressure of 43 cm H2O (or 31.6 mmHg) moved the needle of the pen recorder by 15 mm when the pen recorder was set at 500 mV/cm. To accommodate recording of high intrauterine pressures, the sensitivity of the system could be halved or quartered by setting the pen recorder at 1v/cm or 2v/cm. The paper speed was set to run at 2 mm/minute in all cases. A mark was make on the paper whenever treatment was administered and whenever the sensitivity of the system was changed during the recording.
Calculation of uterine activity.

Intrauterine pressure was recorded and analysed in all groups on Days 1 and 3. A qualitative difference in the pattern of uterine activity was noted on Day 3 in Group 3 (see results) and it was decided to quantify uterine activity in addition to measuring intrauterine pressure in recordings following gemeprost given to mifepristone pretreated women. The unit of quantification used was the Montevideo Unit as described by Caldeyro-Barcia et al (Caldeyro-Barcia et al, 1957). It is a product of strength and frequency of uterine activity measuring a mean increase in intrauterine pressure above baseline pressure multiplied by the number of contractions in a 10 minutes time period. Although the Montevideo Unit was designed to quantify uterine activity in term labour, it has been used (sometimes in combination with other units of measure) by some authors to measure uterine activity following mifepristone and epostane (a 3β hydroxysteroid dehydrogenase inhibitor) in early first and second trimester pregnancy (Swahn & Bygdeman, 1988; Selinger, 1988; Norman et al, 1991a and b; Webster et al, 1985a). The system described by Norman et al was used to define a contraction in this study (Norman et al, 1991a). This system provides a method of objectively identifying a contraction and minimises observer bias. Any increase in uterine activity which lasts for more than one minute is not considered a contraction but rather a change in baseline tone and, therefore, not included in calculation of Montevideo units. An increase in tone is considered a contraction only if its amplitude is more than twice that of the variability around the baseline, so excluding electrical "noise". Episodes of increased intrauterine pressure where pressure dips towards the baseline but does not reach it before rising to a further peak is considered as two contractions only if the difference between the pressure trough and the baseline is less than 20% of the difference between the smaller peak and the baseline. Otherwise, this is considered one contraction (if lasting for less than 1 minute) with the higher peak being taken as the amplitude of the contraction.

Statistics.

The mean or geometric mean and 95% confidence intervals or range of data are quoted unless otherwise stated and were calculated using the Statview Programme (Apple Macintosh). The effects of assigned treatment and of time after treatment on intrauterine pressure and uterine activity were determined by analysis of variance using Newman-Keuls procedure (CLR ANOVA programme, Apple Macintosh). One level (individual time points) comparisons were also made using CLR ANOVA programme. The data were log transformed prior to analysis of variance. Comparison of patient characteristics was made using a t-test save for hCG where a Mann-Whitney test was used (Statview - Apple Macintosh).
Results.

The characteristic of the patients recruited to the study are shown in Table 4.1. There were no significant differences between any parameters studied.

Group 1.

Following passage of the pressure catheter there was no bleeding in any of the women. Bleeding was induced in all women 3 (3, 8) [median (range)] hours following administration of the gemeprost pessary on day 3, 51 (51,56) hours following the start of the study period. No woman required analgesia and none of the women aborted. At follow-up one week later, three women were found to have continuing pregnancies and two women to have missed abortions (Table 4.2). There was no difference in the pattern of uterine activity between Day 1 and Day 3 during the first 30 minutes of recording.

There was no increase in intrauterine pressure with time following insertion of the pressure catheter on Day 1. Analysis of the effect of time on intrauterine pressure after gemeprost administration revealed a significantly greater intrauterine pressure at 60 (p <0.05), 90 (p <0.01), 120 (p <0.01) and 150 (p<0.05) minutes when compared with 0 minutes. In addition, intrauterine pressure was also significantly greater at 90 (p <0.01), 120 (p <0.05) and 150 (p <0.05) minutes compared with 30 minutes following pessary administration (Table 4.3).

Analysis of the effect of assigned treatment (pressure catheter alone versus gemeprost) on intrauterine pressure did not reveal a significant difference in intrauterine pressure when all time points were compared simultaneously. However, comparisons at individual time points showed intrauterine pressure to be significantly greater at 60 and 90 minutes following gemeprost on Day 3 compared with Day 1 (p <0.05).

Group 2.

The median onset of bleeding was 4 (3,54) [median (range)] hours following the first pessary on Day 1. Three women bled during the first 24 hours, 3, 4 and 8 hours following the first pessary. One woman was noted to have vaginal bleeding prior to the insertion of the pressure catheter on Day 3 and one woman commenced bleeding four hours following the administration of the second pessary. One woman required oral dihydrocodeine for analgesia three hours following pessary insertion on Day 1. Complete abortion was induced in two women and at follow-up two women were found to have collapsed gestational sacs on ultrasound and one woman a missed abortion (Table 4.2).
Table 4.1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 5)</th>
<th>Group 2 (n = 5)</th>
<th>Group 3 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>27.4 (21.4 - 31.2)</td>
<td>31.2 (21.4 - 41.0)</td>
<td>34.9 (41.9 - 53.8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.4 (162.1 - 166.7)</td>
<td>163.2 (161.0 - 165.4)</td>
<td>165.3 (162.1 - 166.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.4 (48.6 - 74.2)</td>
<td>62.6 (56.7 - 68.5)</td>
<td>62.2 (50.8 - 66.8)</td>
</tr>
<tr>
<td>Gestation (Days)</td>
<td>49.2 (45.0 - 53.4)</td>
<td>49.4 (45.1 - 53.3)</td>
<td>49.2 (45.0 - 53.4)</td>
</tr>
<tr>
<td>*Parous (No.)</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>+hCG at recruitment (mU/1)</td>
<td>34700 (18870, 96100)</td>
<td>34500 (19580, 66300)</td>
<td>34700 (18870, 96100)</td>
</tr>
</tbody>
</table>

Data show mean (95% confidence intervals), number of patients.*

*Data show mean (95% confidence intervals), number of patients.*
<table>
<thead>
<tr>
<th>Group</th>
<th>0-51</th>
<th>3-54</th>
<th>51-56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Data presented as median (range).*
### Table 4.3

<table>
<thead>
<tr>
<th>Time After Assigned Treatment (minutes)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong> (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 1</strong> (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrauterine pressure in mmHg (geometric mean and 95% C.I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 minutes</td>
<td>18.6-128.0</td>
<td>72.4</td>
<td>72.4</td>
<td>78.1</td>
<td>78.1</td>
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<tr>
<td>30 minutes</td>
<td>19.8-143.7</td>
<td>93.8</td>
<td>93.8</td>
<td>110.0</td>
<td>110.0</td>
<td>110.0</td>
</tr>
<tr>
<td>60 minutes</td>
<td>20.0-157.5</td>
<td>125.4</td>
<td>125.4</td>
<td>142.0</td>
<td>142.0</td>
<td>142.0</td>
</tr>
<tr>
<td>90 minutes</td>
<td>21.2-168.5</td>
<td>157.8</td>
<td>157.8</td>
<td>175.2</td>
<td>175.2</td>
<td>175.2</td>
</tr>
<tr>
<td>120 minutes</td>
<td>22.4-180.0</td>
<td>189.9</td>
<td>189.9</td>
<td>208.4</td>
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<td><strong>Group 2</strong> (n=5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Day 1</strong> (Gemeprost)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intrauterine pressure in mmHg (geometric mean and 95% C.I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 minutes</td>
<td>18.0-35.8</td>
<td>26.1</td>
<td>26.1</td>
<td>31.7</td>
<td>31.7</td>
<td>31.7</td>
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<tr>
<td>30 minutes</td>
<td>19.1-42.7</td>
<td>27.6</td>
<td>27.6</td>
<td>33.2</td>
<td>33.2</td>
<td>33.2</td>
</tr>
<tr>
<td>60 minutes</td>
<td>20.1-49.4</td>
<td>33.7</td>
<td>33.7</td>
<td>40.3</td>
<td>40.3</td>
<td>40.3</td>
</tr>
<tr>
<td>90 minutes</td>
<td>21.2-56.3</td>
<td>39.2</td>
<td>39.2</td>
<td>46.8</td>
<td>46.8</td>
<td>46.8</td>
</tr>
<tr>
<td>120 minutes</td>
<td>22.3-63.3</td>
<td>45.9</td>
<td>45.9</td>
<td>53.5</td>
<td>53.5</td>
<td>53.5</td>
</tr>
<tr>
<td><strong>Group 3</strong> (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 1</strong> (Mifepristone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrauterine pressure in mmHg (geometric mean and 95% C.I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 minutes</td>
<td>17.8-52.4</td>
<td>26.1</td>
<td>26.1</td>
<td>31.7</td>
<td>31.7</td>
<td>31.7</td>
</tr>
<tr>
<td>30 minutes</td>
<td>19.1-42.7</td>
<td>27.6</td>
<td>27.6</td>
<td>33.2</td>
<td>33.2</td>
<td>33.2</td>
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<tr>
<td>60 minutes</td>
<td>20.1-49.4</td>
<td>33.7</td>
<td>33.7</td>
<td>40.3</td>
<td>40.3</td>
<td>40.3</td>
</tr>
<tr>
<td>90 minutes</td>
<td>21.2-56.3</td>
<td>39.2</td>
<td>39.2</td>
<td>46.8</td>
<td>46.8</td>
<td>46.8</td>
</tr>
<tr>
<td>120 minutes</td>
<td>22.3-63.3</td>
<td>45.9</td>
<td>45.9</td>
<td>53.5</td>
<td>53.5</td>
<td>53.5</td>
</tr>
</tbody>
</table>

Note: The table shows the intrauterine pressure in mmHg at various time points after assigned treatment for different groups. The values are expressed as geometric means and 95% confidence intervals (C.I.).
Time was found to exert a significant effect on intrauterine pressure following gemeprost on Day 1 and Day 3. On Day 1 intrauterine pressure was significantly greater at 60 (p < 0.05), 90 (p < 0.05), 120 (p < 0.05) and 150 (p < 0.05) minutes compared with 0 minutes and at 90 (p < 0.05) compared with 30 minutes. On Day 3 the intrauterine pressure was significantly greater at 30, 60, 90, 120 and 150 minutes (all p < 0.01) compared with 0 minutes and at 60, 90, 120 and 150 minutes (all p < 0.01) compared with 30 minutes (Table 4.3).

Analysis of the effect of treatment (gemeprost versus gemeprost following gemeprost pretreatment) on intrauterine pressure showed there to be no significant difference in intrauterine pressure when all time points were compared simultaneously and no significant difference when compared individually.

**Group 3.**
Bleeding was induced in all women prior to administration of gemeprost pessary. The median onset was 41 (26, 48) hours [median range] following mifepristone. Three women required paracetamol for analgesia 2, 3 and 4 hours following pessary insertion respectively. All women aborted completely (Table 4.2). There was no increase in intrauterine pressure with time following mifepristone. However, time exerted a significant effect on intrauterine pressure on Day 3 following gemeprost administration with a significantly higher intrauterine pressure at 30 (p < 0.05), 60 (p < 0.01), 90 (p < 0.01), 120 (p < 0.01) and 150 (p < 0.01) minutes compared with 0 minutes. Intrauterine pressure was significantly greater at 60, 90, 120, 150 minutes (p < 0.01) than at 30 minutes (Table 4.3).

Analysis of the effects of treatment (mifepristone Day 1 versus gemeprost Day 3) showed a greater intrauterine pressure on Day 3 following gemeprost when all time points were compared simultaneously (p < 0.05). When time points were compared individually there was no significant difference between Day 1 and Day 3 intrauterine pressure at 0 minutes. Intrauterine pressure was significantly greater on Day 3 at 30 (p < 0.05), 60 (p < 0.005), 90 (p < 0.005), 120 (p < 0.01), 150 (p < 0.05) minutes.

**All Groups.**
When all groups were considered together, time exerted a significant effect on: Group 1 on Day 3 (gemeprost) [p < 0.001]; Group 2 on Day 1 (gemeprost) [p < 0.005] and Day 3 (gemeprost) [p < 0.05]; Group 3 on Day 3 (gemeprost) [p < 0.001].
Analysis of the effects of assigned treatment when all groups were considered, showed intrauterine pressure to be significantly greater on Day 3 in Group 3 than in all other groups (p <0.05 and p <0.01 compared with Group 1, Day 1) when all time points were compared simultaneously. Intrauterine pressure on Day 3, Group 3, was significantly greater at 30 (p <0.05), 60 (p <0.005), 90 (p <0.05), 120 (p <0.05) and 150 (p <0.05) minutes when individual time points were compared with other groups.

**Measurement of Uterine Activity.**

In addition to having significantly higher intrauterine pressures, women on Day 3 Group 3 were found to have a qualitative difference in uterine activity. In Group 3 all women demonstrated regular small amplitude contractions during the 30 minutes preceding prostaglandin. Following prostaglandin there was an increase in frequency and amplitude of this uterine activity which was sustained for the three hour recording period. In Group 2, only two recordings revealed periods of regular uterine activity. One recording demonstrated regular uterine contractions 30 minutes following gemeprost administration on Day 1 which were sustained for the remainder of the recording period. The other recording demonstrated regular contractions 120 minutes following gemeprost on Day 1 sustained for the remainder of the recording. In both cases the frequency and amplitude of contractions was qualitatively less than in Group 3 on Day 3. In view of the markedly different pattern of uterine activity recorded in Group 3 on Day 3, these tracings were analysed for uterine activity in addition to uterine tone. Montevideo units were used for quantification as previously described (Norman et al, 1991a). Figures 4.1, 4.2 and 4.3 show examples of the patterns of uterine activity in Groups 1, 2 and 3 on Days 1 and 3.

In Group 3 uterine activity increased significantly with time following prostaglandin administration. Uterine activity between 0 and 30 minutes was significantly greater than that during the 30 minutes preceding prostaglandin administration (p <0.05) and uterine activity was also significantly greater 30 to 60, 60 to 90, 90 to 120, 120 to 150 and 150 to 180 minutes following gemeprost compared with the 30 minutes preceding prostaglandin (p <0.01). During time periods 90 to 120 and 120 to 150 minutes, uterine activity was significantly greater than that during the 0 to 30 minute time period (p <0.05) - see Table 4.4.
Day 1 (Control) Paper speed 2mm / minute Amplitude 1v / cm (5mm = 20mm Hg)

Day 3 (Gemeprost Pessary) Paper speed 2mm / minute Amplitude 1v / cm (5mm = 20mm Hg)
FIGURE 4.2
Day 1 (mifepristone) Paper speed 2mm/minute Amplitude 1v/cm (5mm = 20mm Hg)

Day 3 (Gemeprost Pessary) Paper speed 2mm/minute Amplitude 1v/cm (5mm = 20mm Hg)
<table>
<thead>
<tr>
<th>Time after gemeprost (minutes)</th>
<th>Uterine activity in Montevideo units (Geometric mean and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-30 - 0</td>
<td>653.2p, 491.7p, 851.5p, 701.7p, 633.6p, 403.1p, 232.5p</td>
</tr>
<tr>
<td>0 - 30</td>
<td>232.5p, 189.2p, 120 - 150</td>
</tr>
<tr>
<td>30 - 60</td>
<td>90 - 90, 120 - 150</td>
</tr>
<tr>
<td>60 - 90</td>
<td>0 - 30, 0 - 30</td>
</tr>
</tbody>
</table>

* Group 3, Day 3, during 30 minute time intervals before and after gemeprost administration.
* c = greater than 0.05
* b = greater than 0.01
* a = greater than 0.05

Table 4.4
Discussion.
It would appear from this study that pretreatment with the prostaglandin analogue, gemeprost, does not increase the uterine contractile response to further prostaglandin administration 48 hours later. It may be that the initial prostaglandin impact was not great enough. However, bleeding was induced in 4 of the 5 women prior to the administration of the second pessary on Day 3, implying that there was some prostaglandin-mediated damage subsequent to the first dose of gemeprost. In addition, intrauterine pressure rose significantly following gemeprost on Day 1 and, in view of the fact that plasma levels of the analogue are maintained for at least six hours following vaginal administration (Dimov et al, 1983), it is likely that this increase in intrauterine pressure was sustained for some time after the end of the three hour recording period.

The insertion and presence of an intrauterine pressure transducer had no immediate effects on uterine activity with no change in intrauterine pressure being elicited on Day 1. The response to gemeprost on Day 3 did not differ from the response in Group 2 on Day 1 or 3, with a significant increase in intrauterine pressure following prostaglandin administration.

It should be noted that while measurements of intrauterine pressure did not differ between Group 1 and Group 2, treatment outcomes did. Fetal death was induced in 2 of the 5 women in Group 1 with the remaining 3 women being found to have continuing pregnancies at follow up. In contrast, fetal death was induced in all 5 women in Group 2 with two women in this group having successfully induced complete abortions, reflecting perhaps the cumulative effects of gemeprost administration.

The contractile response to gemeprost following mifepristone pretreatment was similar to that reported previously by other authors. In this study intrauterine pressure was significantly higher following gemeprost when women had been pretreated with mifepristone. In addition, the pattern of uterine activity was qualitatively different. In all women in Group 3 there were regular, small amplitude contractions during the 30 minutes prior to prostaglandin administration. In Group 1 and Group 2 the women did not exhibit this pattern of uterine activity prior to prostaglandin on Day 3. Following prostaglandin administration there were sustained, frequent, high amplitude contractions in Group 3. This pattern of uterine activity was distinguishable even during the first 30 minutes after the gemeprost was inserted when plasma levels of the analogue are known to be low (Dimov et al, 1983). Bygdeman and Swahn were the first to note this uterine response to mifepristone and prostaglandin, recording uterine
contractility prior to and after sulprostone injection in mifepristone pretreated women (Bygdeman & Swahn, 1985). The same response of the mifepristone pretreated early uterus has been elicited by gemeprost (Swahn & Bygdeman, 1986), oral 9-methylene PGE2 (meteneprost) (Swahn et al, 1990) and oral misoprostol (Norman et al, 1991b) but not by oxytocin (Swahn & Bygdeman, 1988) or oral PGE2 (Swahn et al, 1989).

In this study the Montevideo unit was used as a measure of uterine activity. Quantification of the uterine activity prior to and following gemeprost in Group 3 showed a significant increase in uterine activity which rose to a maximum at 120 to 150 minutes and subsequently fell slightly. Bygdeman and Swahn subjectively noted that the response of the mifepristone pretreated uterus to prostaglandin analogue, sulprostone, increased with increasing doses of prostaglandin (Bygdeman & Swahn, 1985) and this gradual increase in uterine activity in Group 3 may either reflect increased absorption of gemeprost with time, or merely the effect of time. The uterine activity quantified in Montevideo units in this study is very similar to results obtained by Swahn and Bygdeman using Montevideo units to measure uterine activity following increasing doses of sulprostone (0.05 to 0.15 mg over a 90 minute period) given to women who had received 48 hours of mifepristone pretreatment (Swahn & Bygdeman, 1988). Norman et al reported slightly lower results when misoprostol (200 to 600 µg) was used following mifepristone pretreatment. Uterine activity during the 30 minutes prior to gemeprost was very similar to that reported by Swahn and Bygdeman in the same treatment period but higher than that reported by Norman et al (Swahn & Bygdeman, 1988; Norman et al, 1991a).

It is apparent from the findings of this study that pretreatment with mifepristone elicits a quite different uterine response from pretreatment with gemeprost. Forty eight hours following the antigestagen, regular uterine activity is found. This is not the case 48 hours following prostaglandin administration. The uterine response to exogenous prostaglandin is greatly enhanced by mifepristone pretreatment but prostaglandin pretreatment does not result in such a response to further prostaglandin administration, with no difference being detected in intrauterine pressure or pattern of uterine activity on Day 3 in Group 2 compared with Day 1.

The findings can be interpreted in several ways. It may be that the initial prostaglandin impact in Group 2 was insufficient to disturb what Csapo has described as "the uterine balance" (Csapo, 1977) with no resultant endogenous prostaglandin release. Alternatively, Csapo's theory of prostaglandin impact may be wrong and exogenous prostaglandins, therefore, induce abortion purely by their oxytocic properties.
Neither of these explanations seems likely when the outcome of the pregnancies in Groups 1 and 2 is considered. Two out of five women receiving a single dose of gemeprost (Group 1) were found to have non-viable pregnancies at follow up while all women in Group 2 sustained marked prostaglandin-mediated damage to the conceptus resulting in non-viable pregnancies in three and abortion in two.

The most likely explanation of the different patterns of uterine activity observed is that the enhanced uterine response to exogenous prostaglandins subsequent to mifepristone pretreatment is not mediated solely by endogenous prostaglandin release. It has been shown that in vivo pretreatment with mifepristone reduces the in vitro ability of the chorion, myometrium and decidua of the pregnant guinea pig to metabolise prostaglandins to inactive metabolites (Kelly & Buckman, 1990) and in vivo administration of the antigestagen to women in early pregnancy increases the PGE: metabolite ratio of cultured decidual explants when compared to control tissue. (Norman et al, 1991b). Treatment with mifepristone in vivo significantly reduces the usually high concentration of prostaglandin dehydrogenase (PGDH) in first trimester human decidua with a disappearance of the enzyme from around the blood vessels of the decidua (Cheng et al, 1993a) and increased concentrations of PGE are found in the perivascular region of human decidua after in vivo treatment with the antigestagen (Cheng et al, 1993b). A decrease in PGDH activity and reduced catabolism of prostaglandin in early pregnant human decidua provides an explanation for a lower threshold for uterine stimulation by exogenous oxytocics.

While an alteration in the catabolism of endogenous prostaglandin must play a part in the generation of the enhanced response to exogenous oxytocics of the mifepristone pretreated uterus, it is not the only mechanism responsible for this. Norman et al have shown that indomethacin, a prostaglandin synthetase inhibitor, does not inhibit mifepristone-induced uterine activity in early pregnancy (Norman et al, 1991a). Myometrial activity is increased in pregnant rats treated with mifepristone prior to an increase in the local concentration of uterine PGE$_2$ and PGF$_2\alpha$ (Arkaravichien & Kendle, 1992). Following treatment with onapristone, late pregnant guinea pigs have an increased response to exogenous oxytocin in the absence of any increase in the concentration of myometrial oxytocin receptors (Chawlisz et al, 1991). This last finding is associated with a marked increase in myometrial gap junctions.
Myometrial gap junctions, which are necessary for the generation of co-ordinated uterine activity, have also been shown to be increased in pregnant rat myometrium following mifepristone treatment (Garfield & Baulieu, 1987) and significantly increased levels of transcripts encoding for Connexin-43, the myometrial gap junction protein, have been found in mifepristone-treated pregnant rats (Petrocelli & Lye, 1993).

It seems probable that both these mechanisms are involved in the enhanced response of the mifepristone-treated pregnant uterus to exogenous oxytocic agents and they explain the differences in uterine response observed in this study.

In summary, pretreatment with a gemeprost pessary in early pregnancy does not sensitise the uterus to exogenous prostaglandin administered 48 hours later. Pretreatment with the antigestagen mifepristone, however, greatly enhances the response. The reasons for this observed increase in uterine activity are not certain but endogenous prostaglandin release is unlikely to be the sole mechanism.
CHAPTER 5.

BLOOD LOSS FOLLOWING INDUCTION OF EARLY ABORTION WITH MIFEPRISTONE AND GEMEPROST.
Introduction.

In Chapters 2 and 3 the efficacy and acceptability of early abortion induced by mifepristone and gemeprost was investigated. The results of the studies described in these Chapters suggest that medical termination of early pregnancy using these agents is, in general, a safe procedure. However, one woman in the study in Chapter 2 required haemostatic curettage and another woman, in the study in Chapter 3, required both haemostatic curettage and blood transfusion. In addition, the concentration of haemoglobin was consistently found to fall following treatment. This finding of a fall in haemoglobin after treatment has been reported in other studies and does not appear to be influenced by the dose or manner of administration (single or multiple doses) of mifepristone, or the dose or type of prostaglandin E analogue used (UK Multicentre Trial, 1990; Swahn & Bygdeman, 1989; WHO, 1989; Thong & Baird, 1992; Peyron et al, 1993; WHO, 1993; Henshaw et al, 1994; Thonneau et al, 1995).

Medical induction of early abortion is usually limited to the first seven or eight weeks of amenorrhoea. This time limitation is exerted not only because the incidence of incomplete abortion increases with increasing gestational age, but also because of concern that excessive uterine bleeding may occur, either as an acute event during the passage of fetus and placenta or chronically with continued loss over several weeks (Bygdeman et al, 1976b). For a method of medical abortion to be applicable outwith the context of a clinical trial it must be demonstrated to be safe as well as effective. Many trials have attested to the safety of mifepristone in combination with prostaglandin but none have studied measured blood loss in a large number of consecutively treated women. Instead, safety with regard to blood loss has been measured indirectly by rates of haemostatic curettage and blood transfusion. In a well-nourished, low parity population, these extremes of blood loss are the most relevant to safety. However, in populations where iron deficiency anaemia is endemic lesser degrees of blood loss, which are not reflected by curettage or transfusion rates, could potentially compromise health.

In this Chapter, onset and duration of bleeding and measured blood loss following induction of abortion with mifepristone and gemeprost are studied in 222 consecutively treated women. Included in this number are 13 women of \( \geq 56 \text{ days} < 63 \text{ days} \) amenorrhoea.
Methods.
Two hundred and twenty two consecutive women undergoing medical termination of pregnancy with mifepristone and gemeprost were asked to collect all sanitary wear in order that a measure of blood loss could be made using the alkaline haematin method described by Hallberg and Nilsson (Hallberg & Nilsson, 1964). Women participating in this study included those described in Chapters 2 and 3 and, in addition, women taking part in a UK multicentre trial - the results of which have been reported elsewhere (UK Multicentre Trial, 1990). The inclusion and exclusion criteria and recruitment procedures are as detailed in Chapter 2. For those women forming a part of the multicentre trial, inclusion was extended to women with pregnancies of less than 63 days. All women had grounds for termination under the provision of the 1967 Abortion Act. Local Ethical Committee approval had been granted for the study and written, informed consent was obtained from each woman prior to participation.

Abortion was induced with a combination of mifepristone and gemeprost vaginal pessary. Women received 400 mg, 500 mg or 600 mg mifepristone orally on the first day of treatment. Forty eight hours later women were given either a half 1 mg gemeprost pessary, with the second half administered three hours later, or a whole 1 mg gemeprost pessary. The prostaglandin was administered vaginally into the posterior fornix of the vagina. Women were discharged from hospital at least four hours following prostaglandin and returned for review 1, 2 and 4 weeks following treatment. Follow up was completed following the onset of the next menstrual period before which time non-hormonal methods of contraception (excluding IUCD) were used. Details of recruitment and follow up observations and investigations have been given in Chapters 2 and 3. Women kept a daily record of vaginal blood loss and were instructed to collect all soiled sanitary towels and tampons. In addition, all sanitary wear, blood soiled incontinence pads and blood passed during treatment with mifepristone and gemeprost in hospital were collected.

Measurement of Blood Loss.
Pads, tampons and incontinence pads were added to a molar solution of sodium hydroxide. They were thoroughly mixed and left to soak for 48 hours. An aliquot of liquid was then taken from around the pads and tampons and filtered. Its optical density was measured at 550 nm. Measured loss was calculated by comparing this with the optical density of a 1 ml venous blood sample (taken at the first follow up visit) which had been added to 99 mls of molar sodium hydroxide, left for 24 hours then treated in the same manner as the pads, using the formula:
Optical density 550 nm of pad and tampon eluate x V*
Optical density 550 nm of venous blood x 100.
* Where v = volume of molar sodium hydroxide in which sanitary wear was soaked.

The method had been previously validated in the laboratory and details of this validation are given in Cameron, 1987 (MD Thesis Page 20 – See Appendix II)

**Additional Investigations and Observations.**

Blood was taken for estimation of haemoglobin concentration at recruitment and at follow up one week after treatment, from all women. Measurement of haemoglobin levels was performed by the Haematology Laboratory of the Royal Infirmary of Edinburgh. In addition to a recruitment ultrasound scan, 113 consecutive women (all receiving 600 mg mifepristone) underwent a pelvic ultrasound scan (Diasonics, DRF 250 series) with 7.5 mHz vaginal probe (BMS Scotland, Bothwell, Strathclyde, UK) just prior to prostaglandin administration on day 3. The gestational sac was measured in three diameters and these measurements were entered into the formula, $4/3 \pi r^3$, from which the volume of the gestational sac was derived.

**Statistics.**

Data are expressed as median (range) or mean (standard error) dependent on distribution. The Mann Whitney U test was used for non-parametric comparison and the t-test (for independent and paired samples) for comparison of normally distributed data. Categorical data were compared using the Chi square test. A backwards, stepwise, multiple regression analysis was performed on data to determine the strongest predictor of measured blood loss (Mendenhall, Schaeffer & Wackerely, *Mathematical Statistics with Applications*, p. 451). Height, weight, gestation, parity, change in haemoglobin concentration, duration of bleeding, gestational sac volume, measured blood loss were considered. The cube root of gestational sac volume was taken in order to reduce the wide variation of this variable. Blood loss measurements were log transformed to generate normally distributed data. Pearson's correlation co-efficients were calculated between each of the variables. Due to a high correlation between gestational age and gestational sac volume, both of these variables could not be included in the multiple regression analysis. Gestational age was the variable allowed in the model. The backwards, stepwise, multiple regression, therefore, initially allowed for all previously listed variables with the exception of gestational sac volume.
The Statworks and Statview 512 programmes for Apple Macintosh computer were used for calculation and I acknowledge the help of Dr Peter Thomas (Roussel Laboratories, Uxbridge, UK) with the multiple regression analysis.

**Results.**

Details of treatment outcome and incidence of pad collection are given in Table 5.1. Complete abortion was induced in 218 of 222 women using a combination of mifepristone and gemeprost. Of the 13 women ≥ 56 days and < 63 days amenorrhoea, 13 aborted completely. There were no continuing pregnancies and details of treatment failure have been given in Chapters 2 and 3.

Nine women have been excluded from the analysis of measured blood loss. Two women aborted following mifepristone (both received 600 mg) but prior to gemeprost and in 7 women sanitary wear collection was incomplete.

Table 5.2 gives details of characteristics of women included in the analysis of measured blood loss, grouped according to dose of mifepristone ingested, dose of gemeprost given (both < 56 days amenorrhoea) or gestation ≥ 56 days < 63 days amenorrhoea. There were no significant differences between the three groupings in age, height, weight or parity. Mifepristone and gemeprost groups < 56 days amenorrhoea did not differ significantly in gestation. Gestational sac volume was significantly greater in women of ≥ 56 days < 63 days amenorrhoea (p < 0.001) (Table 5.2).

The median time interval to bleeding following mifepristone did not significantly differ between the groups and in all groups the median onset preceded prostaglandin administration. The median duration of bleeding following treatment was shorter in women receiving 500 mg mifepristone but this was not statistically significant. In all groups there was a large range in the duration of bleeding with some women continuing to bleed for more than three weeks. In women < 56 days amenorrhoea there was no significant difference between the groups in change of haemoglobin concentration (recruitment and first follow up). Women of ≥ 56 days < 63 days amenorrhoea had a significantly greater fall in haemoglobin levels ( p < 0.01) (Table 5.3).
### Table 5.1: Treatment outcome and sanitary wear collection following mifepristone and gemeprost.

<table>
<thead>
<tr>
<th>Dose of Gestation mifepristone (mg)</th>
<th>Number of Women (n)</th>
<th>Complete Abortion (%)</th>
<th>Complete Sanitary Wear (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;56</td>
<td>33 (91%)</td>
<td>125</td>
<td>97</td>
</tr>
<tr>
<td>&gt;56 - 63</td>
<td>12 (100%)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>&gt;63</td>
<td>20 (99%)</td>
<td>61</td>
<td>41</td>
</tr>
<tr>
<td>&gt;75</td>
<td>10 (100%)</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>&gt;95</td>
<td>7 (91%)</td>
<td>7</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose of Gemeprost (mg)</th>
<th>Half Pessary (n)</th>
<th>Whole Pessary (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;63</td>
<td>26</td>
<td>72</td>
</tr>
<tr>
<td>&gt;63</td>
<td>103</td>
<td>13</td>
</tr>
<tr>
<td>&gt;75</td>
<td>103</td>
<td>12</td>
</tr>
<tr>
<td>&gt;95</td>
<td>97</td>
<td>12</td>
</tr>
</tbody>
</table>

*Table 5.1: Treatment outcome and sanitary wear collection following mifepristone and gemeprost.*
<table>
<thead>
<tr>
<th>Dose of mifepristone ((&lt; 56) days amenorrhoea)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>27.1 ± 2.2</td>
<td>166.1 ± 1.3</td>
</tr>
<tr>
<td>27.0 ± 0.6</td>
<td>164.3 ± 0.6</td>
</tr>
<tr>
<td>26.6 ± 0.6</td>
<td>164.1 ± 0.5</td>
</tr>
</tbody>
</table>

Data show mean ± standard error for parity which shows percentage and sac volume which shows median (range). *p < 0.001

<table>
<thead>
<tr>
<th>Dose of gemeprost ((&lt; 56) days amenorrhoea)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Half pessary</td>
<td>Whole pessary</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>27.0 ± 0.4</td>
<td>164.3 ± 0.6</td>
</tr>
<tr>
<td>26.6 ± 0.4</td>
<td>164.1 ± 0.5</td>
</tr>
<tr>
<td>27.1 ± 2.2</td>
<td>166.1 ± 1.3</td>
</tr>
</tbody>
</table>

Data show mean ± standard error for parity which shows percentage and sac volume which shows median (range). *p < 0.001
Table 5.3. Time interval following mifepristone administration to onset of bleeding, duration of bleeding, change in haemoglobin concentration following treatment.

<table>
<thead>
<tr>
<th>Dose of mifepristone</th>
<th>Onset of bleeding (hours)</th>
<th>Duration of bleeding (days)</th>
<th>Change in Haemoglobin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;56 d amenorrhoea</td>
<td>45.6 (20.8, 57.2)</td>
<td>4.5 (2.4, 5.3)</td>
<td>-0.8 ± 0.3*</td>
</tr>
<tr>
<td>56 d &gt; 63 days</td>
<td>33.6 (9.7, 54.8)</td>
<td>13.5 (6.0, 18.0)</td>
<td>-0.3 ± 0.1</td>
</tr>
<tr>
<td>64 d &gt; 63 days</td>
<td>33.1 (21.5, 44.5)</td>
<td>12.5 (8.2, 17.0)</td>
<td>-0.3 ± 0.1</td>
</tr>
<tr>
<td>65 d &gt; 90 days</td>
<td>34.2 (9.7, 54.8)</td>
<td>12.0 (8.0, 17.0)</td>
<td>-0.8 ± 0.3*</td>
</tr>
<tr>
<td>91 d &gt; 120 days</td>
<td>33.9 (21.5, 44.5)</td>
<td>12.5 (8.2, 17.0)</td>
<td>-0.3 ± 0.1</td>
</tr>
</tbody>
</table>

* p < 0.01

Onset of bleeding and duration of bleeding are shown as median (range) and changes in haemoglobin as mean ± standard error.
Overall bleeding started 34.8 (9.71, 58.2) [median (range)] hours following mifepristone and continued for 13 (3, 44) [median (range)] days following treatment. There was a small though highly statistically significant fall in haemoglobin concentration from 12.9 g/dl to 12.5 g/dl between recruitment and follow up seven days after treatment (p < 0.0001) (Table 5.4).

When measured blood loss results of women < 56 days amenorrhea were grouped according to dose of mifepristone, there was found to be no significant difference between women receiving 400 mg, 500 mg or 600 mg of mifepristone. Overall the median loss was 72 mls (Table 5.5).

Division of results (< 56 days amenorrhoea) according to the amount of prostaglandin administered revealed a median loss of 70 mls after a half 1 mg gemeprost pessary and 75 mls after a whole 1 mg gemeprost pessary. These results were not statistically significantly different (Table 5.6).

Table 5.7 shows the results of blood loss grouped according to gestational age. When grouped in this manner, blood loss increased significantly with increasing amenorrhoea at the time of treatment. Overall, the median loss was 74 mls. A backwards, stepwise, multiple regression analysis was performed on data to determine the strongest predictor of measured blood loss. Height, weight, gestation, parity, change in haemoglobin concentration, duration of bleeding, gestational sac volume, measured blood loss were considered. The cube root of gestational sac volume was taken in order to reduce the wide variation of this variable. Blood loss measurements were log transformed to generate normally distributed data. Pearson’s correlation co-efficients were calculated between each of the variables. Due to a high correlation between gestational age and gestational sac volume, both of these variables could not be included in the multiple regression analysis. Gestational age was the variable allowed in the model. The backwards, stepwise, multiple regression, therefore, initially allowed for all previously listed variables with the exception of gestational sac volume.

Table 5.8 shows the variables between which correlation co-efficients were calculated. There was found to be no correlation between height, weight, parity or duration of bleeding and measured blood loss.

Table 5.9 shows comparisons of variables which were found to be significantly correlated.
Table 5.4  Onset of bleeding following misoprostol treatment, duration of bleeding after treatment, haemoglobin concentration before and after treatment (all women considered n = 213).

<table>
<thead>
<tr>
<th>Onset of Bleeding (hours)</th>
<th>Duration of Bleeding (days)</th>
<th>Haemoglobin before (g/dl)</th>
<th>Haemoglobin after (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4 ±0.1</td>
<td>1.2 ±0.1</td>
<td>12.5 ±0.1</td>
<td>12.9 ±0.1</td>
</tr>
</tbody>
</table>

* p < 0.0001

Data show median (range) and mean ± standard error.
<table>
<thead>
<tr>
<th>Dose of mifepristone (mg)</th>
<th>Measured Blood Loss (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>72.0 (14.312)</td>
</tr>
<tr>
<td>158</td>
<td>70.0 (14.512)</td>
</tr>
<tr>
<td>12</td>
<td>82.5 (19.123)</td>
</tr>
<tr>
<td>30</td>
<td>71.5 (15.339)</td>
</tr>
</tbody>
</table>

Data show median (range).

> 56 days amenorrhea

Table 5.5

 Measured Blood Loss (dose of mifepristone given).

All
<table>
<thead>
<tr>
<th>Dose of gemeprost (&lt; 56 days amenorrhoea)</th>
<th>Measured Blood Loss (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Pessary</td>
<td>Data show median (range)</td>
</tr>
<tr>
<td>109</td>
<td>75.0 (15.447)</td>
</tr>
<tr>
<td>91</td>
<td>70.0 (14.512)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALL</th>
<th>Measured Blood Loss (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>91</td>
</tr>
</tbody>
</table>

Measured Blood Loss (dose of prostaglandin given).
<table>
<thead>
<tr>
<th>Gestation (days of amenorrhoea)</th>
<th>Measured Blood Loss (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>3</td>
</tr>
<tr>
<td>36-42</td>
<td>28</td>
</tr>
<tr>
<td>43-49</td>
<td>69</td>
</tr>
<tr>
<td>50-56</td>
<td>57.5</td>
</tr>
<tr>
<td>51-56</td>
<td>28</td>
</tr>
<tr>
<td>57-60</td>
<td>7</td>
</tr>
<tr>
<td>&gt;60</td>
<td>19.0 (19, 31)</td>
</tr>
<tr>
<td>ALL</td>
<td>213</td>
</tr>
</tbody>
</table>

Data show median (range).

* p < 0.05 Significance of difference from preceding value.

+ p > 0.05
Table 5.8 Variables for which correlation coefficients were calculated.

- Height.
- Weight.
- Gestation.
- Parity.
- Duration of bleeding.
- Gestational sac volume.
- Change in haemoglobin.
- Measured blood loss.
Measured blood loss was found to be correlated with gestational age, gestational sac volume and change in haemoglobin concentration. Figure 5.1 shows measured loss plotted against gestation. Untransformed data have been used for clarity.

The backwards, stepwise, multiple regression analysis allowed initially for all variables in Table 5.8 with the exception of gestational sac volume. The model was reduced to include the effects of gestational age and change in haemoglobin concentration only. Both these variables were found to have highly significant effects in the model (p <0.001).

```
log y = 10^{2.84} X - 46.98    r = 0.3
```
<table>
<thead>
<tr>
<th>Variables</th>
<th>Significance</th>
<th>r</th>
<th>0.001 &gt; d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured blood loss - v - gestational sac volume</td>
<td>-0.43</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Measured blood loss - v - gestational sac volume</td>
<td>-0.3</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Measured blood loss - v - gestational sac volume</td>
<td>0.3</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Weight - v - height</td>
<td>0.3</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Weight - v - height</td>
<td>0.71</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Gestational age - v - gestational sac volume</td>
<td>0.0</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Measured blood loss - v - change in haemoglobin concentration</td>
<td>0.0</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.9 Comparisons found to have a correlation coefficient, r, < 0.25.
Discussion.
The median blood loss measured in the 200 women in this study of <56 days amenorrhoea was 72 mls. The dose of mifepristone did not influence blood loss. Several other dose finding studies have found this directly and indirectly. Chan et al measured blood loss in women receiving 200 mg, 400 mg or 600 mg mifepristone prior to gemeprost 1 mg and found no significant difference between the three groups. However, the median loss (84.1, 99.9 and 101.4 mls respectively) was larger than that measured in this study (Chan et al, 1993). A smaller study of blood loss following 25 mg mifepristone 12 hourly on five occasions or 600 mg mifepristone once followed by gemeprost 1 mg also found no significant difference between different doses of antigestagen but also reported a higher median measured loss of 91.5 mls overall (Prasad et al, 1995). Indirect assessment of blood loss by calculation of the change in concentration of haemoglobin seven days following abortion has confirmed the lack of influence of dose of mifepristone on blood loss. Studies of 200 mg, 400 mg and 600 mg mifepristone or 25 mg mifepristone 12 hourly on five occasions and 600 mg mifepristone once followed by gemeprost 1 mg show no difference between groups in the level of fall in haemoglobin concentration (WHO, 1993; 1991). The amount of prostaglandin administered did not influence measured blood loss in this study.

Cameron et al, found that the addition of prostaglandin to treatment with mifepristone made little difference to the amount of measured blood loss with a median loss of 62 mls when mifepristone was used alone compared with 81 mls when used in combination with gemeprost (Cameron et al, 1986). Bygdeman and Swahn in an early study of mifepristone and sulprostone, reported a subjective impression of smaller blood loss when prostaglandin was used in conjunction with the antigestagen. However, the study in this Chapter would suggest, in agreement with Cameron et al, that prostaglandin exerts little effect on actual blood loss. A doubling of the amount of prostaglandin used in this study had no effect on measured blood loss which was similar in amount to that recorded by Kovacs et al and Cameron et al, using mifepristone alone (Kovacs et al, 1984; Cameron et al, 1986).

The measured blood loss in women of less than 56 days amenorrhoea in this study is similar to measured loss reported following early abortion with E series prostaglandin analogues alone and vacuum aspiration. Bygdeman et al, reported a 62 to 78 ml loss with meteneprost (Bygdeman et al, 1981; 1983). Smith and Baird found the measured loss following gemeprost (87 mls) to be much the same as that following vacuum aspiration under local (72 mls) or general (85 mls) anaesthetic. In all these studies the median blood loss was comparable with that of a heavy menstrual period,
roughly 80 mls. It is of note that in this study there is a large range in the results and some women lost considerably more than 80 mls. Other smaller studies of blood loss following early abortion with mifepristone and gemeprost have found a higher median loss (Chan et al, 1993; Prasad et al, 1995).

Hamberger et al studied blood loss following early abortion with 15-methyl-PGF$_2\alpha$ vaginal pessaries and found the average loss to be 121 mls, higher than that following abortion with either E series analogues, mifepristone alone or a combination of the two. The findings of a Chinese Multicentre Trial support the theory that blood loss is heavier when F series analogues are used in early pregnancy. Ji et al studied the effects of mifepristone 600 mg oral in combination with dl-15-methyl PGF$_2\alpha$ methyl ester 1 mg vaginal pessary for the induction of abortion in 160 women of less than 49 days amenorrhoea. Although no actual measure of blood loss was made, 61.5% of women felt that the bleeding was "much more abundant" than their menses and haemoglobin concentrations fell from a mean 13.2 g/dl at recruitment to 12.5 g/dl at follow up (Ji et al, 1988).

The mean fall in haemoglobin concentration was 0.4 g/dl in this study and other studies of mifepristone in combination with gemeprost have reported similar results: Chan et al found a fall of 0.1 to 0.2 g/dl (Chan et al, 1993), Norman et al 0.1 g/dl (Norman et al, 1992), WHO and Henshaw et al 0.2 to 0.3 g/dl (WHO, 1993; Henshaw et al, 1994). Larger falls in haemoglobin have been found when the antigestagen is used in combination with other E series analogues. Thonneau et al reported a 0.7 g/dl fall when 250 mg of sulprostone was used and Thong and Baird reported the same 0.7 g/dl decrease when misoprostol 600 µg was administered (Thonneau et al, 1995; Thong & Baird, 1992b).

Comparisons of medical termination using mifepristone and prostaglandin with vacuum aspiration have been made in terms of blood loss. Chan et al found measured loss to be significantly less following vacuum aspiration (53 vs 84 to 101 mls) (Chan et al, 1993). Thonneau et al reported a 0.7 g/dl fall in haemoglobin concentration following mifepristone and sulprostone but no change in haemoglobin concentration following vacuum aspiration (Thonneau et al, 1995). Henshaw et al, however, found no significant difference in the fall in haemoglobin between women undergoing medical abortion with mifepristone and gemeprost or vacuum aspiration (Henshaw et al, 1994).
Mifepristone and gemeprost were found to be effective in inducing complete abortion up to 63 days of amenorrhea in this study. All 13 women treated between 56 and 63 days aborted completely. The fall in haemoglobin concentration following treatment in this group of women, however, was significantly greater than in women whom treatment was restricted to less than 56 days amenorrhea. Henshaw et al have found medical abortion using mifepristone and gemeprost less acceptable after 50 days amenorrhea because of pain (Henshaw et al, 1993). It may be that this method of pregnancy termination is most applicable to earlier gestations.

In this study there was found to be no correlation between blood loss and parity. Although studies of measured loss following early medical abortion with E series analogues have not examined the effect of parity on blood loss, Hamberger et al found a high positive correlation between parity and measured blood loss when abortion was induced with 15-methyl PGF2\(_\alpha\) vaginal pessaries (Hamberger et al, 1978).

The most important determinants of the amount of measured blood loss in this study were change in haemoglobin concentration and gestational age. The former provides indirect validation of this way of measuring blood loss - the latter confirms the impression of increased blood loss with increasing gestation gained when results are grouped according to gestation. Although the combination of mifepristone and gemeprost was effective irrespective of gestation, the blood loss was significantly greater as the period of amenorrhea increased. It is likely that as pregnancy advances and the fetus and placenta increase in size, there is a larger vascular area from which bleeding can occur. Moreover, retention of trophoblastic tissue is common following both medical and surgical abortion and in Chapters 2 and 3 the continued presence of trophoblast was suggested by the detection of hCG in serum up to four weeks following abortion. Hamberger et al, found a strong positive correlation between slow decline in hCG levels and, by implication, greater amounts of retained trophoblast, and heavier blood loss (Hamberger et al, 1978). It seems probable that more trophoblast will be retained as gestation increases and this may also account for the increased blood loss observed with advancing gestation. It should be noted that gestation is not an infallible predictor of blood loss, however, and some women of early gestation do bleed heavily (see Figure 5.1).

The strong correlation of gestational sac volume and gestational age has practical relevance and demonstrates that where access to ultrasound facilities is not possible, menstrual history combined with vaginal examination, will predict gestational age with sufficient accuracy.
The duration of bleeding following abortion in this study was not correlated with total subsequent blood loss. In cases where bleeding is prolonged, it is usually scant and previous studies of blood loss following abortion with prostaglandins have shown that the highest daily loss occurs within the first four days of treatment, with blood loss between the 5th and 14th days after treatment representing less than one-third of the total loss (Bygdeman et al, 1981; 1983).

In conclusion, although mifepristone used in combination with gemeprost effectively induces complete abortion up to 63 days gestation, the fall in haemoglobin concentration is significantly greater after 56 days amenorrhoea. In addition, measured blood loss increases with increasing gestation and the findings of this study would suggest that induction of abortion with the antigestagen and prostaglandin analogue, should be limited to less than 56 days amenorrhoea. Although the median loss before 56 days amenorrhoea is 72 mls, some women bleed significantly more heavily than this and, therefore, this method of abortion requires both skilled medical supervision and access to surgical facilities.
CHAPTER 6.

THE EFFECTS OF PRETREATMENT WITH 600 MG OF MIFEPRISTONE ON INDUCTION OF MIDTRIMESTER ABORTION WITH GEMEPROST PESSARIES.
Introduction.
The use of stable E series prostaglandin analogues provides a means of non-invasive induction of midtrimester abortion which avoids the hazards of intrauterine administration of prostaglandins. Despite the availability of these compounds induction of midtrimester abortion remains a long and unpleasant procedure. Whether natural prostaglandins are instilled intra- or extra-amniotically or prostaglandin analogues are given intramuscularly or vaginally, around 20% of women will not abort within the first 24 hours of treatment.

Pretreatment with various agents in the second trimester has been shown to reduce the prostaglandin induction-abortion time interval and increase cumulative 24 hour abortion rates. The percentage of women aborting within 24 hours can be increased to over 90% if laminaria tent is used before the administration of gemeprost (Takagi et al, 1982), sulprostone (Karim et al, 1982; Bygdeman & Christensen, 1983) or 15-methyl PGF2α free acid (Bygdeman & Christensen, 1983). If epostane (a 3βHSD inhibitor) is given to women for three days prior to extra-amniotic prostaglandin E2 instillation, induction - abortion intervals are reduced by around 50% (Selinger, 1988). Similarly, pretreatment with 200 mg of mifepristone 24 hours before extra-amniotic prostaglandin E2 instillation results in a 25% reduction in the prostaglandin induction - abortion interval (Urquhart & Templeton, 1987).

In this Chapter the effects of pretreatment with 600 mg mifepristone, 36 hours before induction of midtrimester abortion with gemeprost pessaries, are studied in 100 women of between 12 and 18 weeks of pregnancy.

Methods.
One hundred women of between 12 and 18 weeks of pregnancy were recruited to the study. All women had previously been counselled by two doctors and scheduled for midtrimester abortion under the provision of the 1967 Abortion Act.

Local Ethical Committee approval was granted for the study and written, informed consent was obtained from each woman prior to recruitment after detailed verbal and written information had been given.

Recruitment.
A full history and general examination was performed. A pelvic ultrasound scan was performed to confirm gestation. Blood was taken for estimation of haemoglobin concentration and blood group typing.
Exclusion criteria for the study were -

- less than 16 years of age.
- less than 12 weeks or greater than 18 weeks of pregnancy.
- abnormal pregnancy including history of threatened abortion, multiple pregnancy, intrauterine death, fetal abnormality.
- more than two previous spontaneous abortions.
- current or past medical history of serious respiratory, cardiovascular, neurological, endocrine or gastrointestinal disease.
- contraindications to mifepristone or prostaglandin administration.

Following recruitment women were serially allocated by random number table to receive three oral tablets of either 3 x 200 mg mifepristone (n=50) or 3 x placebo (n=50). All tablets were identical in appearance including packaging. Randomisation was performed by Roussel Laboratories UK Limited and patients and investigator were blind to the randomisation.

**Administration of mifepristone or placebo.**

Prior to administration of the tablets women were asked about the incidence of vaginal bleeding, pelvic pain, headache, tiredness, anorexia, hot flushes, nausea, vomiting, diarrhoea, dysuria, faintness and indigestion. Temperature, blood pressure and pulse rate were recorded, height and weight were measured. No dietary restrictions were imposed. Tablets were swallowed with water. Following administration of tablets, women were questioned hourly for four hours about the incidence of the previously listed symptoms or the occurrence of any others. Hourly recordings of temperature, blood pressure and pulse rate were made for four hours. Women were then allowed to go home.

**Prostaglandin administration.**

All women were re-admitted to hospital 36 hours following tablet ingestion. On admission, they were asked about the incidence of all the previously listed symptoms and the occurrence of any others. Temperature, blood pressure and pulse rate were measured. All women were then given a 1 mg gemeprost vaginal pessary inserted into the posterior fornix of the vagina. This treatment was repeated 3-hourly until either abortion had occurred or a maximum of five pessaries had been given. Women who did not abort within 24 hours of the first pessary were prescribed a further course of up to five gemeprost pessaries. If abortion had not occurred within 48 hours of the first pessary, an intravenous infusion of oxytocin was
commenced and escalated to a maximum of 64 mU/minute. If satisfactory uterine activity could not be induced with the maximum infusion rate of oxytocin, additional prostaglandin was given following discussion with the woman's consultant.

Women remained supine for one hour following the insertion of each 1 mg gemeprost pessary. An intravenous infusion of crystalloid was commenced prior to the insertion of the first pessary and although oral fluids were allowed, solid foods were withheld. Women were questioned every three hours, at the time of pessary insertion, regarding the incidence of the previously listed symptoms. Blood pressure, temperature and pulse rate were measured three hourly. Prophylactic medication was not given but analgesia and antiemetics were prescribed when required. 7.5 mg intramuscular diamorphine was given for pain and 50 mg intramuscular cyclizine for vomiting.

Following abortion, an intramuscular injection of syntometrine (ergometrine maleate 500 µg and oxytocin 5IU) was given to all women. Evacuation of the uterus was performed, if this was felt necessary by the woman's consultant (or a member of her consultant medical team).

Rhesus negative women were given anti-D prophylaxis prior to discharge from hospital. All women were given an appointment for follow up four to six weeks later. All women were allowed home once contraception had been supplied or appropriate contraceptive advice given. Each woman was asked to keep a record of vaginal bleeding.

**Follow Up Visit.**

Women were asked about relevant medical intervention or symptoms since discharge from hospital. The record of vaginal bleeding was reviewed. Vaginal examination was performed to ensure that the uterus had involuted and that the cervix was closed. A blood sample was taken for estimation of the level of haemoglobin. Women were discharged from the study after this visit.

**Blood Samples.**

Haemoglobin concentration was measured by the Haematology Laboratory, Royal Infirmary of Edinburgh.

**Ultrasound Scans.**

Pelvic ultrasound scans for assessment of gestation were performed by the Ultrasound Department of Simpson Memorial Maternity Pavilion, Edinburgh.
Data Calculation and Statistics.
When follow up had been completed on all women, the data were recorded on data sheets. The randomisation code was then broken.

Normally distributed data are shown as mean ± standard error and data which were not normally distributed are shown as median (range). Categorical data were analysed using the Chi square test. Non-parametric comparisons of non-normally distributed data were made using the Mann Whitney U test. Normally distributed data were compared using a t-test for paired or independent samples. The Statworks and Statview 512 programmes for the Apple Macintosh computer have been used for calculation.

Results.
The characteristics of the women treated are shown in Table 6.1. There were no statistically significant differences between the two groups. Table 6.2 lists the incidence of various symptoms during the 36 hours following tablet ingestion but prior to prostaglandin administration. Three women who had received mifepristone reported the incidence of minimal vaginal bleeding prior to prostaglandin administration. This had commenced approximately 24 hours following tablet ingestion and did not exceed vaginal spotting. Pelvic pain was commonly reported by both groups with 17 (34%) of women receiving mifepristone and 10 (20%) of women receiving placebo experiencing mild dysmenorrheic-like discomfort. Headaches and tiredness were also common in both groups. However, significantly more women who had received mifepristone reported the incidence of nausea and vomiting during the first 36 hours of treatment (p <0.05).

One woman has been excluded from the analysis of treatment outcome following gemeprost administration. She received her first pessary 51 hours following tablet ingestion (mifepristone 200 mg x 3). She required two 1 mg gemeprost pessaries to induce abortion and the prostaglandin induction - abortion interval was 5 hours and 10 minutes. During this time she required two intramuscular injections of diamorphine and vomited twice. She underwent surgical evacuation of the uterus following abortion and failed to attend for follow up.

Table 6.3 details the treatment outcome of the other 99 women. Of the 49 women in Group I (mifepristone) 46 (94%) aborted within 24 hours of the insertion of their first gemeprost pessary. Two women required more than five pessaries both using a total of seven pessaries. Only one woman failed to abort with prostaglandin alone and needed an infusion of oxytocin to induce abortion.
Data show mean ± standard error except for parity which shows number (percentage).

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (mifepristone)</th>
<th>GROUP II (placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.5 ± 0.6</td>
<td>21.9 ± 0.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.2 ± 0.9</td>
<td>161.1 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.9 ± 1.1</td>
<td>60.5 ± 1.5</td>
</tr>
<tr>
<td>Parous (%/weeks)</td>
<td>14 (28%)</td>
<td>17 (34%)</td>
</tr>
</tbody>
</table>

n = 50

Table 6.1: Patient Characteristics.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>GROUP I (mifepristone)</th>
<th>GROUP II (placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 50</td>
<td>n = 50</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pain</td>
<td>17 (34%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (34%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>13 (26%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10 (20%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Hot Flushes</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (28%)*</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (20%)*</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Faintness</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Indigestion</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

* p < 0.05  Data show number (%)
<table>
<thead>
<tr>
<th>GROUP</th>
<th>Abortion within 24 hours</th>
<th>Abortion within 48 hours</th>
<th>Oxytocin Infusion</th>
<th>Additional Prostaglandin</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 49)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>10 pessaries</td>
<td></td>
</tr>
<tr>
<td>II (n = 50)</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05

Table 6.3

Treatment outcome following gemeprost administration.
In Group 2, of the 50 women who had received placebo, 40 (80%) aborted within 24 hours of their first pessary. This was a significantly smaller proportion than in the mifepristone pretreated group (p <0.05). Four women required a total of 6, 8, 9 and 10 pessaries respectively to induce abortion and four women needed an infusion of oxytocin to induce abortion. Two women required additional prostaglandin to induce abortion, one receiving a further five gemeprost pessaries and one an intra-amniotic PGE2 and urea instillation.

Figure 6.1 shows the cumulative abortion rate of both groups of women. Pretreatment with mifepristone was found to greatly reduce the prostaglandin induction-abortion interval (Table 6.4). The prostaglandin induction - abortion interval was only 6.8 hours when mifepristone pretreatment had been given and 15.8 hours when placebo had been given (p <0.0001). Pretreatment with mifepristone also significantly reduced the amount of prostaglandin required to induce abortion with three as opposed to five pessaries being used (p <0.0001). Table 6.5 details analgesic used during gemeprost administration.

Overall the use of intramuscular opiate analgesia was significantly less in mifepristone pretreated women (1.1 injections per woman vs. 1.5 injections per woman, p <0.05). However, requirement of analgesia per pessary did not differ between the two groups.

There was no significant difference between parous and primiparous women in either group in the use of opiate analgesia with 11 (65%) parous and 28 (88%) primiparous women in the mifepristone group requiring diamorphine and 11 (79%) parous and 27 (75%) primiparous women in the placebo group requiring diamorphine.

The incidence of vomiting and diarrhoea during treatment with gemeprost is shown in Table 6.6.

There was no significant difference in incidence of gastro-intestinal side effects between the two groups. Of the 20 women vomiting in Group I, the mean number of episodes was 2.8. In Group II, the mean number of episodes of vomiting in 20 women was three. Only five women in Group I and 10 in Group 2 experienced diarrhoea with a mean 4 and 2.1 episodes respectively. Overall, there was a mean 1.2 episodes of vomiting in each group and a mean 0.4 episodes of diarrhoea in each group.
Table 6.4

<table>
<thead>
<tr>
<th>Group</th>
<th>Prostaglandin Induction - Abortion</th>
<th>Number of Pessaries Given</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>(2.0, 67.8)*</td>
<td>(1.10)</td>
<td>(2.0, 67.8)*</td>
</tr>
<tr>
<td></td>
<td>(5.9, 93.6)</td>
<td>(1.10)</td>
<td>(5.9, 95.6)</td>
</tr>
<tr>
<td></td>
<td>15.8</td>
<td>3</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Data show median (range) with p < 0.0001: Group I > Group II.

Number of pessaries administered prior to abortion:

- Group I: (2.0, 67.8)*
- Group II: (5.9, 93.6)
Table 6.5

Analgesic use during treatment with gemeprost.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mifepristone (n = 49)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.4 ± 0.0</td>
<td>0.3 ± 0.0</td>
</tr>
<tr>
<td>II</td>
<td>1.4 ± 0.1*</td>
<td>1.5 ± 0.2</td>
</tr>
</tbody>
</table>

Data show mean ± standard error. *p < 0.05

Injections of diamorphine per woman per pessary.
<table>
<thead>
<tr>
<th>GROUP</th>
<th>Mifepristone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20 (41%)</td>
<td>20 (41%)</td>
</tr>
<tr>
<td>II</td>
<td>5 (10%)</td>
<td>10 (20%)</td>
</tr>
</tbody>
</table>

Number of women vomiting.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Mifepristone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.8</td>
<td>4.1</td>
</tr>
<tr>
<td>II</td>
<td>2.1</td>
<td>4</td>
</tr>
</tbody>
</table>

Mean episodes per woman vomiting.

Gastrointestinal side effects during treatment with gemeprost.
Figure 6.1
Cumulative abortion rate of Group I (mifepristone) and Group II (placebo)
The majority of women underwent surgical evacuation of the uterus following abortion and there were no significant differences in the incidence of complete or incomplete abortion between the two groups (Table 6.7). One woman in the placebo group required a 2-unit transfusion of red cell concentration following an episode of heavy vaginal bleeding which occurred during surgical evacuation of the uterus.

Women pretreated with mifepristone had a significantly shorter stay in hospital (Table 6.8) spending a median one night in hospital compared with two when given placebo (p <0.05).

Forty three women (88%) from Group I and 41 (82%) women from Group II attended for follow up. Details of this visit are given in Table 6.9.

There was no significant difference in the duration of bleeding following abortion between the two groups. The haemoglobin concentration was found to have increased following abortion in both groups though this was only statistically significant in Group I.

Only one woman required hospital re-admission following abortion. She had been pretreated with mifepristone. She was found clinically to have pelvic inflammatory disease and an ultrasound scan revealed retained products of conception. Chlamydia trachomatis was isolated from an endocervical swab. She underwent re-evacuation of the uterus with appropriate antibiotic cover.

Five women in Group I and six women in Group II received antibiotics in treatment of offensive vaginal discharge. Culture of endocervical swabs yielded growth of a variety of pathogenic organisms (β haemolytic streptococcus, bacteroides, trichomonas vaginalis).
<table>
<thead>
<tr>
<th>Group</th>
<th>Mifepristone (n=49)</th>
<th>Placebo (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete abortion</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Incomplete abortion</td>
<td>15 (31%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Retained placenta</td>
<td>26 (53%)</td>
<td>36 (72%)</td>
</tr>
<tr>
<td>Surgical evacuation of uterus</td>
<td>45 (92%)</td>
<td>48 (96%)</td>
</tr>
</tbody>
</table>

**Table 6.7**

Incidences of complete abortion, incomplete abortion, and retained placenta.
Table 6.8 Length of stay in hospital.

<table>
<thead>
<tr>
<th>GROUP I</th>
<th>GROUP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>mifepristone</td>
<td>placebo</td>
</tr>
<tr>
<td>(n = 49)</td>
<td>(n = 50)</td>
</tr>
</tbody>
</table>

Nights spent in hospital.

1 (1,5)*         2 (1,5).

Data show median (range) * p < 0.05
Table 6.9: Follow-up attendance, duration of bleeding following abortion, haemoglobin concentration before and after abortion.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Mifepristone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>43 (88%)</td>
<td>41 (82%)</td>
</tr>
<tr>
<td>Returning (%)</td>
<td>12.2 ± 0.2*</td>
<td>12.2 ± 0.2*</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>12 (3.41)</td>
<td>14 (1.25)</td>
</tr>
<tr>
<td>Haemoglobin before</td>
<td>12.6 ± 0.2*</td>
<td>12.2 ± 0.2*</td>
</tr>
<tr>
<td>Haemoglobin after</td>
<td>12.6 ± 0.2*</td>
<td>12.6 ± 0.2*</td>
</tr>
</tbody>
</table>

Data show number (%), median (range) and mean ± standard error. *p < 0.05
Discussion.
This study has confirmed the findings of Urquhart and Templeton (1987). They achieved a 25% reduction in the prostaglandin induction - abortion interval, when 200 mg of mifepristone was ingested 24 hours prior to a "standard extra-amniotic prostaglandin infusion regime". The median interval to abortion in antigestogen pretreated women was 9.2 hours (Urquhart & Templeton, 1987). The median prostaglandin induction to abortion interval in this study was reduced by 57% to 6.8 hours when women received mifepristone pretreatment. The greater magnitude of decrease in the time interval - abortion is probably due to the longer pretreatment interval: although mifepristone can be shown to have some effect on pregnant uterine activity by 24 hours, this effect is increased by 36 hours (Swahn & Bygdeman, 1988) and in vitro studies of decidual prostaglandin production following mifepristone suggest maximal effects by 36 hours (Smith & Kelly, 1987).

Studies of varying doses of mifepristone administered 36 to 48 hours prior to treatment with gemeprost or misoprostol, another PGE1 analogue, have reported almost identical prostaglandin induction - abortion intervals to this study. Thong and Baird, using a 6 hourly rather than 3 hourly administration of gemeprost preceded by 200 mg mifepristone, induced abortion at a median of 6.6 hours following the first prostaglandin pessary (Thong & Baird, 1992a). Hinshaw et al reported a 6.1 hour prostaglandin induction - abortion interval when 600 mg mifepristone was followed by 800 µg misoprostol per vaginam (pv) and 400 µg misoprostol orally three hourly thereafter (Hinshaw et al, 1995). A reduction in the dose of mifepristone to 200 mg made no difference to the outcome using an identical misoprostol regime with abortion occurring 6.9 hours after first prostaglandin administration (Webster et al, 1996).

The prostaglandin induction-abortion interval following mifepristone pretreatment of 6.8 hours in this study is shorter than that obtained when laminaria pretreatment is used before intramuscular or vaginally administered analogues in the midtrimester (Bygdeman & Christensen, 1983; Takagi et al, 1982). Thong and Baird compared treatment with a 6 hourly gemeprost regimen to treatment with a synthetic tent, dilapan, followed six hours later by 6 hourly administration of gemeprost and to treatment with 200 mg mifepristone followed 36 hours later by gemeprost. Although pretreatment with the antigestagen significantly reduced the induction to abortion interval (6.6 hours), pretreatment with dilapan made no difference with the median interval to abortion being 15.6 hours compared with 15.7 hours when no pretreatment was used (Thong & Baird, 1992a). More recently, Ho et al have compared induction of midtrimester abortion using 600 mg mifepristone followed
36 hours later by gemeprost 1 mg three hourly with laminaria tent followed 12 hours later by the same gemeprost regimen. They found that pretreatment with the antigestagen resulted in a significantly shorter induction - abortion interval (7.5 hours) than pretreatment with laminaria (11 hours) (Ho et al, 1995).

Ninety four per cent of women pretreated with mifepristone in this study aborted within 24 hours of prostaglandin administration compared with 80% of women who received placebo and of the remaining women pretreated with mifepristone only one failed to abort with gemeprost alone. Cameron and Baird obtained a 77% 24 hour cumulative abortion rate using the same regime of gemeprost (Cameron & Baird, 1984b) and in a further study, 82% of women aborted within 24 hours (Cameron et al, 1987). Bygdeman and Christensen reported 98% cumulative 24 hour abortion rates for 15-methyl PGF2α free acid and sulprostone following pretreatment with laminaria. However, prostaglandin was administered throughout the 24 hour period rather than for 12 hours as in this study (Bygdeman & Christensen, 1983).

Thong and Baird reported a cumulative 24 hour abortion rate of 95% when a smaller dose of both mifepristone and gemeprost was used at the same gestation (Thong & Baird, 1992a) and Webster et al using 200 mg mifepristone prior to misoprostol induced abortion in 97% of women within 24 hours (Webster et al, 1996).

The number of gemeprost pessaries required to induce abortion was significantly reduced by mifepristone pretreatment. A median of three pessaries as opposed to five in the placebo group was used. Other authors using gemeprost without pretreatment to induce midtrimester abortion have found a similar pessary requirement as that in the placebo group in this study (Tagaki et al, 1982; Cameron & Baird, 1984b; Sakamoto et al, 1982; Cameron et al, 1987). Although vaginal administration of prostaglandin is undoubtedly safer than intrauterine administration, it is not without risk and cardiovascular collapse has been reported as a complication of gemeprost in the midtrimester of pregnancy (Kalra et al, 1989). A significant reduction in the dose of gemeprost administered reduces the risk of such complications.

Thong and Baird, as previously mentioned, have demonstrated that a reduction in the dose of gemeprost used is possible without having an impact on efficacy. They found a six hourly administration of gemeprost 1 mg to a maximum of four pessaries allowed a median of one pessary to be used to induce midtrimester abortion after mifepristone pretreatment (Thong & Baird, 1992a).
Mifepristone was found to significantly increase the incidence of vomiting and nausea during the 36 hours prior to prostaglandin treatment. Although in early pregnancy there was no significant increase in these symptoms following mifepristone ingestion (Chapters 2 and 3) the high incidence of both vomiting and nausea in early pregnancy makes it more difficult to demonstrate a difference made by the antigestagen. Ho et al also found the antigestagen increased the incidence of nausea and vomiting prior to prostaglandin administration when compared with laminaria pretreatment (Ho et al, 1995).

The incidence of vomiting and diarrhoea was similar in both groups in this study with around 40% of women vomiting and between 10 and 20% experiencing diarrhoea. Bygdeman et al obtained identical results with meteneprost in the second trimester with 40% of women vomiting and 13% experiencing diarrhoea during treatment (Bygdeman et al, 1980b). Cameron et al have reported a much lower incidence of vomiting (14%) using gemeprost three hourly alone (Cameron et al, 1987).

Other studies of midtrimester abortion using mifepristone and comparable prostaglandin regimes report a similar incidence of vomiting and diarrhoea (Webster et al, 1996; Ho et al, 1995). However, Thong and Baird were able to significantly reduce prostaglandin-related gastrointestinal side effects by using less frequent prostaglandin administration (Thong & Baird, 1992a).

The overall use of opiate analgesia was significantly less following mifepristone pretreatment and this was related to reduced prostaglandin use. When analgesic use was studied in terms of requirement for diamorphine per pessary, there was no difference between the two groups.

The rate of surgical evacuation of the uterus was high in this study with the vast majority of women undergoing curettage after abortion, in some cases even when the abortion was felt to be complete. This reflects individual hospital practice. The risks of general anaesthesia are small but tangible and must be balanced against the potential benefit of routine surgical evacuation. In cases of retained placenta it may be beneficial to attempt uterine evacuation with further prostaglandin before resorting to surgery. Other studies report a far higher complete abortion rate (Hinshaw et al, 1995; Webster et al, 1996). Women pretreated with mifepristone had a significantly shorter stay in hospital than those who received placebo. This median of stay of one night in hospital could potentially have reduced further if a different policy had operated regarding surgical evacuation of the uterus.
Only one woman required transfusion during the course of the study and it is of note that the haemorrhage occurred during surgical evacuation of the uterus. Webster et al have also found an association between surgical evacuation of the uterus and haemorrhage, necessitating transfusion, with the only two women out of 70 they studied requiring transfusion being those who bled during surgical evacuation of the uterus (Webster et al, 1996). Apart from the one case of haemorrhage requiring transfusion, there were no serious complications of treatment. Of note, there were no cases of cervical laceration and this is in part attributable to the use of a vaginal and not intra-uterine administration of prostaglandin and a small requirement for oxytocin stimulation.

The mifepristone-primed midtrimester uterus provides a better model for term pregnancy than the early pregnant uterus does. In early pregnancy a luteal source of steroid, a high concentration of high affinity progesterone receptor in the decidua (Padayachi et al, 1989) and marked decidual effects of mifepristone (Chapter 1) make it difficult to extrapolate to late pregnancy. By contrast, in both midtrimester and term pregnancy, steroidogenesis is placental and high affinity progesterone receptors are absent from the decidua (Padayachi et al, 1987) though present in myometrium (Padayachi et al, 1988).

Although it has been suggested that mifepristone could have wide application in term pregnancy for the induction of labour, it appears to have what Chawlisch and Garfield refer to as a "labor conditioning" rather than "labor inducing" effect on animals which do not have a withdrawal of progesterone at term such as guinea pigs, non-human primates and women (Chawlisch & Garfield, 1996). Haluska et al studied the effect of mifepristone on preterm macaques and found an increase in uterine activity and amniotic fluid prostaglandins but no change in cervical dilatation and no induction of labour (Haluska et al, 1987). Treatment with mifepristone failed to induce labour in near-term cynomologous monkeys despite inducing uterine activity and cervical ripening (Wolf et al, 1993). However, the addition of treatment with oxytocin improves the efficacy of labour induction with mifepristone (Wolf et al, 1989).

Oxytocin has been shown to induce delivery more efficiently in guinea pigs following onapristone pretreatment without changing myometrial receptor concentrations and in association with an increase in myometrial gap junctions (Chawlisch et al, 1991). Mifepristone used alone can induce labour in the presence of a dead fetus (Cabrol et al, 1985) but only around 50% of women near term with a live fetus will labour within four days of treatment with the antigestagen (Frydman et al, 1992). Although mifepristone is known to cross the placenta in second trimester human
Mifepristone used alone can induce labour in the presence of a dead fetus (Cabrol et al, 1985) but only around 50% of women near term with a live fetus will labour within four days of treatment with the antigestagen (Frydman et al, 1992). Although mifepristone is known to cross the placenta in second trimester human pregnancy (Frydman et al, 1985; Hill et al, 1990b) and by inference, third trimester human pregnancy and in second and third trimester pregnancy in monkeys (Wolf et al, 1988), there appear to be no significant ill-effects on newborn human (Frydman et al, 1991) and monkey (Wolf et al, 1989) infants, when mifepristone is used to induce labour. Fetal abnormalities have been noted in the rabbit following maternal mifepristone ingestion (Jost, 1986) but this appears to be a function of progesterone withdrawal rather than direct teratogenicity of the antigestagen and Csapo reported similar abnormalities following luteectomy in rats (Csapo, 1969). Reports in human women suggest certainly that early exposure to mifepristone does not affect subsequent fetal wellbeing (Lim et al, 1990).

The effect of mifepristone on fetal cortisol and aldosterone concentrations is uncertain. Hill et al have demonstrated an increase in fetal aldosterone concentrations following maternal ingestion of mifepristone in the midtrimester. Fetal cortisol levels did not increase significantly and it was uncertain whether this represented a lack of antiglucocorticoid effect of mifepristone or a failure of fetal compensation for glucocorticoid blockage (Hill et al, 1990b). Withdrawal of cortisol would be expected to have a detrimental effect on fetal lung maturation and further investigation is required to resolve this issue.

In summary, this study has demonstrated that pretreatment with 600 mg of mifepristone 36 hours before induction of midtrimester abortion with gemeprost significantly reduces the prostaglandin induction - abortion interval. The amount of prostaglandin required to induce abortion is greatly decreased and, in addition, the requirement for opiate analgesia is less. The finding in this study of increased response to prostaglandin following mifepristone pretreatment and the findings of others of the ripening effects of mifepristone on the cervix, suggest that providing it is shown to be without hazard to the fetus, mifepristone will be a useful agent for the induction of labour.
CONCLUSIONS.
The work in this thesis confirms the efficacy and acceptability of mifepristone and gemeprost for the induction of abortion in early and midtrimester pregnancy. Chapter 2 demonstrates that administration of mifepristone as a single, rather than divided dose, simplifies the treatment regime without compromising efficacy. In addition, treatment outcome appeared dose independent with no significant difference being found in abortion rates when 400 mg, 500 mg or 600 mg mifepristone was used in combination with gemeprost. However, the number of women studied was too small to expose minor differences in efficacy. The incidence of side effects, in particular, pain, was low.

The data in Chapter 3 indicate that currently recommended doses of gemeprost, when used in combination with mifepristone, are too high. A significant reduction in the incidence of severe pain was achieved by administering only half of a 1 mg gemeprost pessary, 48 hours following 600 mg mifepristone. There was no significant difference in complete abortion rates between women of < 56 days amenorrhoea receiving a half or a whole 1 mg gemeprost pessary following mifepristone. Overall, 99% of women aborted completely and gastro-intestinal side effects were few, confirming the acceptability of this technique as an alternative to vacuum aspiration.

While clinically it is well accepted that mifepristone sensitises the uterus to exogenous prostaglandins, the reasons for this remain unclear. If Csapo's theory of prostaglandin impact is accepted, the data in Chapter 4 would suggest that this effect of mifepristone is not mediated solely by endogenous prostaglandin release.

In Chapter 5 the safety of early induction of abortion with mifepristone and gemeprost, in terms of blood loss, is confirmed. However, although abortion can be effectively induced by these agents beyond 56 days of amenorrhoea, the significant increase in blood loss and decrease in haemoglobin suggest that treatment is best limited to pregnancies of less than 56 days. In addition, sporadic heavy blood loss can occur at any gestation and medical supervision with access to surgical facilities remains necessary.

The data in Chapter 6 demonstrate the effect of mifepristone on the requirement for prostaglandin to induce midtrimester abortion. As in early pregnancy, the antigestagen increases the midtrimester uterine response to exogenous prostaglandin.
Mifepristone pretreatment results in a greatly reduced prostaglandin induction-abortion interval and decreases the need for opiate analgesia. Assuming it can be shown to cause no ill-effect to the fetus, mifepristone will have wide application as an agent for induction of labour.

In summary, a single dose of 400 to 600 mg of mifepristone in combination with a half or whole 1 mg gemeprost pessary, safely and efficiently induces abortion before 56 days of amenorrhoea causing low side effects. The smallest effective dose of either drug is not yet known. While the mechanism by which mifepristone increases the uterine response to exogenous prostaglandin is not fully understood, it appears to function in both the first and second trimester of pregnancy.

The use of mifepristone in combination with prostaglandin, provides a long awaited alternative to vacuum aspiration and, in addition, improves currently available mid trimester abortion methods.
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APPENDIX 1.

PUBLICATIONS.


INDUCTION OF THERAPEUTIC ABORTION IN EARLY PREGNANCY WITH MIFEPRISTONE IN COMBINATION WITH PROSTAGLANDIN PESSARY

MARY W. RODGER DAVID T. BAIRD
Department of Obstetrics and Gynaecology, Centre for Reproductive Biology, University of Edinburgh, 37 Chalmers Street, Edinburgh EH3 9EW

Summary Therapeutic abortion was induced in 100 women in early pregnancy (less than 56 days' amenorrhoea) with a combination of the antigestagen mifepristone (RU 486) and a synthetic prostaglandin analogue, gemeprost. Mifepristone in oral doses of 400–600 mg was followed 48 h later by a gemeprost vaginal pessary (0.5–1.0 mg). Bleeding was induced in all women 22–70 h after the mifepristone dose and although bleeding continued for 4–43 days (median 12) the total measured blood-loss was only a median of 72.5 ml (range 15–398). Complete abortion occurred in 95 women. Surgical evacuation of the uterus for minimum debris was required in the remaining 5. Only 10 women had diarrhoea or pain that required opioid analgesia. The combination of mifepristone and gemeprost provides a safe and effective alternative to surgical evacuation of the uterus for therapeutic abortion in early pregnancy.

Introduction

In England and Wales in 1986, 172 286 pregnancies were terminated by therapeutic abortion.1 In the first 12 weeks of pregnancy the uterus can be evacuated safely by vacuum aspiration, when the complication rate is related to the length of gestation.2 However, surgical termination requires skilled doctors and nurses and often general anaesthesia.

Before 8 weeks of amenorrhoea spontaneous abortions are frequently complete. If therapeutic abortion with prostaglandin analogues is induced in this stage of pregnancy incomplete abortion is rare with over 90% of women requiring no surgical intervention.3-5 However, the usefulness of these agents is limited by the high frequency of gastrointestinal side-effects, which appears unaffected even by controlled release of prostaglandin per vaginam.6

Mifepristone (RU 486, Roussel), a derivative of the progestagen norethisterone, is a powerful antiprogestrone and antiglucocorticoid, and mild antiandrogen. It binds reversibly at the receptor and has a half-life of about 24 h.7 When used to induce abortion, mifepristone has fewer side-effects than prostaglandin analogues but is less effective, with between 60 and 85% of women aborting completely.8-10 Preliminary reports suggest that the addition of a prostaglandin to treatment with mifepristone increases the efficacy of the antigestagen without major increases in mifepristone side-effects.11,12 We report here our experience with mifepristone in combination with a vaginal pessary containing gemeprost (May & Baker) in 100 women presenting for termination of early pregnancy. Gemeprost is a synthetic prostaglandin E₁ analogue (16, 16-dimethyl-trans-Δ₁-PGE₁, methylester).

Patients and Methods

Patients

Local family-planning services and general practitioners were asked to refer women of less than 56 days' amenorrhoea who had requested termination of pregnancy to the gynaecological outpatient department of the Royal Infirmary of Edinburgh, when it had been established that there were grounds for termination of pregnancy under the 1967 Abortion Act (Scotland). 100 women participated in this open study (table I). Pregnancy was confirmed by measurement of the serum level of human chorionic gonadotrophin (hCG). Gestational age was assessed by an accurate menstrual history, clinical examination, and a pelvic ultrasound scan. Women with evidence of multiple pregnancy or spontaneous abortion were excluded from the study as were those with a history of serious medical disorder and those aged below 17. Local ethical committee approval was granted for the study and written informed consent was obtained from each participant. All women were admitted on the first day of treatment (day 1). No dietary restrictions were imposed.

<table>
<thead>
<tr>
<th>TABLE I—PATIENTS’ CHARACTERISTICS</th>
</tr>
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<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>I (n = 20)</td>
</tr>
<tr>
<td>II (n = 30)</td>
</tr>
<tr>
<td>III (n = 30)</td>
</tr>
<tr>
<td>IV (n = 20)</td>
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</tbody>
</table>

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Treatment

Group I (n = 20) received 150 mg mifepristone orally each day for 4 days (17 of these patients have been reported briefly). Groups II (n = 30), III (n = 30), and IV (n = 20) received a single oral dose of mifepristone, 450 mg, 500 mg, or 600 mg, respectively, between 0900 and 1200 h. In group I half a 1 mg gemeprost vaginal pessary was inserted into the posterior fornix of the vagina 48 h after the first dose of mifepristone; the other half was inserted 6 h later. The first 6 women in group I received a whole 1 mg pessary 48 h after mifepristone administration. The remaining 74 women were given one half-pessary 48 h after mifepristone administration; the rest of the pessary was inserted 3 h later only if there had been no uterine pain or bleeding.

Prophylactic medication was not prescribed. Analgesic drugs were given as required: oral paracetamol or dicydodeclin for mild to moderate pain, intramuscular pethidine (100 mg) or diamorphine (5 mg) for severe pain. Intramuscular cyclazocine was given for vomiting.

Assessments

Samples of peripheral blood were collected at recruitment for measurement of the concentration of haemoglobin, urea, electrolytes, cortisol, and HCG and for liver function tests. Blood was also taken for oestradiol and progesterone assay from all women except those in group I. Each woman recorded symptoms in a diary, from the day before treatment started. Some women were asked to collect all soiled sanitary protection once treatment had started so that blood loss could be estimated.

Women in group I had their temperature, pulse rate, and blood-pressure measured 4 hourly for 12 h after drug administration. The first 10 women in group II had the same observations hourly for 10 h. Because side-effects were few in these 10 women, these observations were made at 1 and 2 h after mifepristone in the remaining women.

The women remained in hospital for at least 3 h after gemeprost administration during which time hourly recordings of temperature, pulse rate, and blood-pressure were made. Patients were discharged once uterine pain and vaginal bleeding had lessened.

Follow-up Visits

The women were reviewed 1, 2, and 4 weeks after treatment and discharged from follow-up after the onset of the next menstrual period. At each visit uterine size and the cervix were assessed. An endocervical swab was taken for culture from women who complained of offensive vaginal discharge. At the first visit blood was collected for estimation of the concentration of haemoglobin, urea, electrolytes, cortisol, and HCG and for liver function tests. Blood was taken for oestradiol and progesterone assay in groups II–IV. At the other visits blood was collected for estimation of HCG concentration in groups II–IV, and urine was collected in group I for an immunological pregnancy test. Abortion was considered complete if by 4 weeks vaginal bleeding had ceased, the cervix was closed, the uterus was normal sized, and either the serum level of HCG was less than 200 mIU/ml or an immunological pregnancy test in urine was negative. 13 of the women in group I, 11 in group II, 26 in group III, and 20 in group IV collected all their soiled sanitary protection.

Hormone Assays

Progesterone and oestradiol were measured by radioimmunoassay. HCG was assayed with commercial reagents (Serono), the lower limit of sensitivity was 3 mIU/ml plasma. Cortisol was measured by radioimmunoassay.

Measurement of Blood-loss

Blood-loss was calculated from used sanitary towels and tampons by a modification of Halberg and Nilsson's method. Soiled sanitary wear was placed in a molar solution of sodium hydroxide for 48 h. A sample of liquid was filtered and its optical density measured at 550 nm. Blood-loss was calculated by comparison with the optical density of 1 ml of peripheral blood placed in a similar sodium hydroxide for 24 h.

Results

The effectiveness of the four treatment regimens was similar (table II). Of the 74 women who received half a gemeprost pessary, only 10 (14%) required the second half. There were no on-going pregnancies and 95 of the women aborted completely. Only 5 women required surgical intervention. In group I, a woman of 48 days' amenorrhoea underwent curettage 6 weeks after treatment because of persistent vaginal spotting and an ultrasound scan suggestive of minimum uterine debris. Her HCG levels had decreased and an immunological pregnancy test in urine was negative. Hysteroscopic examination of the scant curettings revealed necrotic trophoblastic tissue but no fetal parts. In Group II, a woman of 50 days' amenorrhoea was taken to theatre because of brisk vaginal bleeding 5 h after the insertion of half a gemeprost pessary. Under anaesthesia the products of conception were removed from the cervical os with a rapid decrease in blood-loss. She was not shocked and did not require transfusion. 3 women in group III required curettage. 1 woman of 33 days' amenorrhoea underwent surgical evacuation of the uterus 5 weeks after initial treatment; the rest of her history was identical to that of the woman in group I. Another woman of 50 days' amenorrhoea underwent curettage 17 days after treatment because her HCG level fell-out despite a large initial decrease. An ultrasound scan confirmed a small area of retained products of conception. The third woman in this group who underwent curettage was 48 days from her last menstrual period when treated. Her HCG level had fallen appropriately for 2 weeks but at her final visit was found to have increased. Ultrasound revealed minimum uterine debris. Histological examination of the curettings from these 3 patients revealed trophoblastic tissue but no fetal parts.

Because there was no significant difference between the four groups in the onset of bleeding and pain, requirement for analgesia, side-effects, duration of bleeding, measured blood-loss, the time until the next menstrual period, and all

<table>
<thead>
<tr>
<th>TABLE II—OUTCOME OF TREATMENT</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Total (n = 100)</td>
</tr>
</tbody>
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*x2 = 3.81, p < 0.1.*
TABLE IV—NUMBER OF PATIENTS WITH GASTROINTESTINAL SIDE-EFFECTS

<table>
<thead>
<tr>
<th>Day</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>54</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

Significant difference between the days—$t^2 = 22.11$; $p < 0.001$ and $t = 6.89$, $p < 0.05$.

TABLE V—HORMONAL CONCENTRATIONS BEFORE AND AFTER TREATMENT ($n = 80$)

<table>
<thead>
<tr>
<th>Time</th>
<th>HCG (mL/m)</th>
<th>Oestradiol (pg/mL)</th>
<th>Progesterone (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60476 (7420)</td>
<td>5823 (1012)</td>
<td>432 (98)</td>
</tr>
<tr>
<td>48h</td>
<td>1971 (2511)</td>
<td>964 (99)</td>
<td>341 (41)</td>
</tr>
<tr>
<td>Day 26</td>
<td>503 (110)</td>
<td>6.4</td>
<td>26.7</td>
</tr>
</tbody>
</table>

Significant difference compared with before treatment—$t = 10.99$ and $p < 0.001$.

Laboratory results, data were pooled for analysis. Bleeding was induced in all 100 women (table III). Bleeding started 36 h after mifepristone administration and continued for 12 days; the median measured blood-loss of 72 women was 72.5 mL. The haemoglobin concentration was similar before and after treatment. No woman required blood transfusion.

The 94 women who had pain were first aware of pelvic discomfort 46 h (19-5-70) after the start of treatment. The products of conception were identified during the treatment of 57 women at 42 h (2.5-9-2) after insertion of the meproprost pessary. No patient required analgesia during the first 48 h of treatment. After insertion of the pessary, 44 women received an oral analgesic drug and 9 women received an intramuscular opioid. 47 women required no analgesia.

There was no significant difference in the frequency of nausea before and during treatment (table IV). There was, however, a significant increase in the incidence of vomiting and of diarrhoea. 30 women vomited after the pessary was inserted compared with 13 the day before treatment, and 10 women had diarrhoea compared with 3 before treatment. 40 women had pelvic cramps for 2-3 days after treatment. No women had clinical evidence of pelvic infection. 7 women received antibiotics when pathogenic organisms (β-haemolytic streptococcus, Trichomonas vaginalis, gonococcus, Bacteroides) were isolated on culture of an endocervical swab. The interval until the next menstrual period was 31 (14-48) days from treatment.

Liver function tests and cortisol levels were similar before and after treatment. Levels of HCG decreased significantly over the week after treatment although HCG was still detectable in plasma 2 and 4 weeks after treatment (table V). Oestradiol and progesterone also decreased significantly after treatment. There was no significant difference in the results between women who required evacuation and those who did not.

Discussion

Previous studies of mifepristone, when used alone to terminate early pregnancy, have shown an unacceptably high rate of incomplete abortion and ongoing pregnancy.7,8 Although meproprost effectively induces early abortion, the doses required are associated with a high incidence of side-effects such as pain that requires opioid analgesia and vomiting and diarrhoea.4,8 This study has confirmed our preliminary report12 that the addition of a small dose of prostaglandin to treatment with mifepristone increases the frequency of complete abortion. In the present study 95 women aborted completely after treatment with a combination of mifepristone and gemeprost. There were no ongoing pregnancies after treatment. Although 5 women underwent curettage, in retrospect the first 3 probably did not require surgical intervention. As we gained experience we became more confident in disregarding minimum continued vaginal bleeding.

No serious complications were encountered during treatment. Heavy bleeding, attributed to insufficient endogenous prostaglandin production, during treatment with mifepristone alone has been reported.9 However, none of the women in our study required transfusion and haemoglobin concentration did not decrease after treatment. The measured blood-loss was similar to that expected during a heavy period10 and to that after vacuum aspiration and medical termination with gemeprost alone, although the duration of bleeding was found to be slightly longer than with these methods.4,16

The occurrence of pain that required opioid analgesia was low compared with that when prostaglandin analogues are used alone.4 Only 9 of our patients required intramuscular pethidine or diamorphone and almost half the patients needed no analgesic drug at all. Nausea occurred in more than half the patients before and during treatment. Although 30 women vomited after administration of gemeprost, 13 had done so the day before treatment. Nausea and vomiting are common symptoms in early pregnancy, and diarrhoea, a more specifically prostaglandin-related side-effect, occurred in only 10 women. That the occurrence of gastrointestinal side-effects was less frequent than during treatment with gemeprost alone is a reflection of the smaller dose of prostaglandin.

There is evidence that mifepristone sensitises the uterus to the oxytocic action of prostaglandins by releasing endogenous prostaglandins from the decidua.11,12 Clinically this would appear to be the case with mild pelvic pain starting before exogenous prostaglandin administration and a high abortion rate after an otherwise subtherapeutic dose of gemeprost. This combination of mifepristone and gemeprost exploits the advantages of both compounds: a low frequency of side-effects and a high frequency of complete abortion.

There was no difference in the efficacy of the four treatment regimens and the dose of prostaglandin required to achieve complete abortion was not greater when the dose of mifepristone was lower. Kovacs et al17 studied 37 women of less than 42 days' amenorrhoea, after 25, 50, or 100 mg mifepristone twice daily for 4 days, and found that the occurrence of complete abortion was not dose-related. Couziniet al18 treated 100 women within 10 days of their missed period and found no difference in the effectiveness of 400, 600, or 800 mg mifepristone. Our study confirms these findings and also demonstrates the effectiveness of single as opposed to sequential administration of mifepristone.

The comparison of medical termination of pregnancy with vacuum aspiration is not straightforward. The 5% incidence of incomplete abortion after treatment with mifepristone and gemeprost must be weighed against the need for a skilled operator to do vacuum aspiration and, arguably, the need for and therefore risk of a general anaesthetic.19-22 The occurrence of incomplete abortion after medical termination of pregnancy, however, makes careful
follow-up a necessity. Undoubtedly experience leads to a lower rate of surgical intervention, as we found during our study.

Acceptability to the patient is important if medical termination of early pregnancy is to be used as an alternative to surgical abortion. The acceptability of medical termination has been assessed.21 Women who found this type of abortion unacceptable were usually those who had had pain and other side-effects. The use of mifepristone in combination with gemeprost is an effective and safe means of medical induction of therapeutic abortion. The low frequency of severe pain and gastrointestinal side-effects suggest that this is an acceptable means of termination and could provide an alternative to surgical abortion. The combination would have particular application in those countries where skilled medical and surgical experience are in short supply.

The help of Sister A. Michie, Sister H. Hillier, and Sister D. Will in the management of patients is appreciated. We thank Margaret Harper for typing the manuscript and Dr Ian Roberts of Roussel for supplying mifepristone. We also thank local general practitioners and Brook Advisory and Family Planning Centres for their co-operation.

Correspondence should be addressed to D. T. B.

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Prostaglandins and antigestagens for the interruption of early pregnancy

David T. Baird, Mary Rodger, Iain T. Cameron and Ian Roberts*

Department of Obstetrics and Gynaecology, University of Edinburgh, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9EW, U.K. and *Roussel Laboratories Limited, Broadwater Park, North Orbital Road, Uxbridge, Middlesex UB9 5HP, U.K.

Summary. During pregnancy the uterus is maintained in a quiescent state by the secretion of progesterone. Antigestagens antagonize the biological action of progesterone by binding to the nuclear receptor in the target organs. Administration of the antigestagen mifepristone to women induces bleeding during the luteal phase and in early pregnancy by releasing endogenous prostaglandins from the endometrium or decidua. In addition, the sensitivity of the myometrium to exogenous prostaglandins is markedly increased. Although mifepristone will induce bleeding in the majority of women in early pregnancy, the incidence of incomplete abortion or ongoing pregnancies increases with increasing gestational age and is too high to be clinically useful as an agent for therapeutic abortion. However, a single dose of mifepristone (400–600 mg) followed by a vaginal pessary of a prostaglandin analogue (0-5–1-0 mg), gemeprost, induced complete abortion in 95 of 100 women of gestational age <42 days (<56 days amenorrhoea). The incidence of diarrhoea (15%) and abdominal pain requiring opiate analgesia (10%) was much lower than when abortion was induced with prostaglandin alone. Vaginal bleeding continued for 13-8 ± 0-8 days after administration of the prostaglandin. A combination of an antigestagen with a small dose of a prostaglandin analogue is an effective alternative to vacuum aspiration for the therapeutic termination of early pregnancy.

Keywords: man; pregnancy; prostaglandins; antigestagens

Interruption of early pregnancy

In most developed countries in which therapeutic abortion is legal, termination of pregnancy is usually performed before the 10th week of pregnancy (12 weeks amenorrhoea) when it is possible to evacuate the uterus relatively safely by vacuum aspiration (Cates et al., 1979). As the complications of abortion are directly related to the period of gestation, there are considerable advantages in terminating a pregnancy as early as possible. Therapeutic abortion in the first 6 weeks is often referred to as 'menstrual induction'. At this stage many spontaneous abortions are complete and in contrast to more advanced pregnancies the incidence of retained products of conception is low. In this paper we shall compare the various methods for inducing therapeutic abortion in early pregnancy.

Definition of terms

Gestational age refers to the time from conception rather than the usual clinical method referring to the period of amenorrhoea. Therapeutic abortion refers to the interruption of pregnancy by medical
or surgical means before the time of fetal viability (20–26 weeks). We define ‘early abortion’ or menstrual regulation as termination of pregnancy before 42 days (56 days amenorrhea).

The legal status of ‘contraindication’ in the U.K., i.e. the administration of substances post-coitally before the expected menstrual period to prevent implantation of the embryo is uncertain at the moment. The Attorney General has ruled that post-coital oestrogens or gestagens and the intrauterine device are not considered as causing abortion although they clearly do not prevent conception (Havers, 1983; Cook, 1985).

It has been suggested by Baulieu (1985) that ‘contragestion’ be used to describe all means of fertility control including those inhibiting fertilization (contraception) and those which involve inducing very early abortion after implantation, e.g. 14–21 days. However, it is not yet clear whether this would be acceptable legally or ethically as a regular method of fertility regulation.

We shall not consider induction of abortion of gestational age > 42 days although prostaglandins have found widespread application for the induction of abortion in the mid-trimester of pregnancy and antigestagens may have application for pre-operative cervical dilatation.

Physiology of early pregnancy

Within a few days of fertilization the embryo reaches the uterus and implants in the endometrium about Day 7–9. The secretion of progesterone from the corpus luteum is essential for successful implantation and subsequent maintenance of the pregnancy. Progesterone stimulates the production of a variety of proteins from the secretory endometrium which are probably necessary for the recognition and sustenance of the early embryo. In addition the high concentrations of progesterone maintain the myometrium in a quiescent state so that uterine contractility is minimal. A reduction in the concentration of progesterone at any stage in pregnancy results in increased contractility of the uterus due in part to the release of prostaglandins from the decidua (Csapo & Pulkkinen, 1978, for review).

Although the mechanism by which the corpus luteum in the normal cycle undergoes regression is unknown, it is accepted that its maintenance in pregnancy is due to the secretion of hCG by the developing trophoblast. The placenta secretes progesterone from an early stage but the production is insufficient to maintain pregnancy until 35 days at which time the pregnancy will continue after removal of the corpus luteum (Csapo & Pulkkinen, 1978).

There are, therefore, a variety of methods in addition to surgical evacuation of the uterus which could theoretically be used to interrupt early pregnancy.

Luteolytic agents. Any compound which causes regression of the corpus luteum should result in abortion up to 35 days. Unfortunately, no suitable substance which is effective in the presence of hCG has yet been identified.

Antagonists of hCG. Competitive inhibitions or antibodies to hCG should lead to withdrawal of luteotrophic support and hence abortion. Although studies in primates have demonstrated the feasibility of this approach, clinical studies involving immunization of women against the β-subunit of hCG are still at the experimental stage (Talwar et al., 1987).

Oxytocic substances. The uterus is relatively insensitive to oxytocin in early pregnancy, probably due to a scarcity of oxytocin receptors (Fuchs et al., 1982). However, prostaglandins will induce powerful uterine contractions and induce abortion although many preparations have undesirable side effects (see later).

Inhibition of progesterone. Because the maintenance of pregnancy is dependent on progesterone, inhibition of its synthesis, e.g. by administration of an inhibitor (epostane) of the enzyme 3β-ol dehydrogenase will result in abortion (Webster et al., 1985). However, progesterone is a key intermediate in the synthesis of steroids by the adrenal gland and hence such a compound could lead to adrenocorticotrophic insufficiency (van der Spuy et al., 1983). A more attractive approach is the antagonism of the action of progesterone at the target organ. By binding to the nuclear progesterone receptors in
the myometrium and endometrium the receptor complex is deformed and unable to bind to nuclear DNA so that the action of endogenous progesterone is prevented (Baulieu et al., 1987).

Mifepristone (RU 486; Roussel, Uxbridge, U.K.) is a synthetic steroid similar in structure to norethindrone but with a dimethylaminophenyl group (17β-hydroxy-11β (4-dimethylaminophenyl) 17α-(1-propynyl) oestra-4,9 diene-3-one) substituted at the 11 position in the steroid nucleus. In vitro, mifepristone binds to androgen and glucocorticoid receptors as well as the progesterone receptor. When given to normal non-pregnant volunteers there is a compensatory increase in the secretion of ACTH and cortisol such that the amount of free cortisol is almost unchanged (Bertagna et al., 1984). No cases of adrenocorticoid insufficiency have been described during its short-term administration (up to 7 days) for induction of abortion. After a single dose administered orally the absorption is rapid and the concentrations in plasma remain elevated for several days due to the long half-life (about 20 h) (Heikinheimo et al., 1987).

Spontaneous abortions occurring after 8 weeks of amenorrhoea are usually incomplete and the uterus requires surgical evacuation. Early clinical studies demonstrated that abortion could be induced following the administration of mifepristone alone to women in the first 10 weeks of pregnancy (Herman et al., 1982; Kovacs et al., 1984; Vervest & Haspels, 1985). However, in about 30% of women the abortion was incomplete or failed and one woman who bled heavily required emergency blood transfusion and evacuation of the uterus. For these reasons we have restricted our studies of induction of abortion by medical means alone to gestational age <42 days.

In this paper we shall review our clinical experience with mifepristone, the first antigestagen which has become available for clinical trials for induction of abortion. The efficacy, safety and side effects of mifepristone and a synthetic prostaglandin analogue, gemeprost, alone or in combination, will be compared to the conventional method of vacuum aspiration.

Subjects and methods

Women of less than 56 days amenorrhoea requesting therapeutic termination of pregnancy under the 1967 Abortion Act were recruited for trials of medical abortifacients. After it had been determined that therapeutic abortion was indicated women were asked whether they would be prepared to take part in randomized trials of surgical versus various medical means of inducing abortion. Initially, vacuum aspiration under local or general anaesthesia was compared to a prostaglandin analogue (gemeprost: 16,16 trans δ3 dimethyl prostaglandin E1 methyl ester: May & Baker, Dagenham, Essex, U.K.) in the form of 1 mg vaginal pessaries in Witepsol base (Smith & Baird, 1980). When only gemeprost was used, up to 3 pessaries were inserted in the vagina every 3 h. Further studies were conducted comparing vacuum aspiration with mifepristone or gemeprost pessaries alone or in combination (Cameron et al., 1986; Rodger & Baird, 1987; Cameron & Baird, 1988). Mifepristone was given orally in doses of 400, 500 or 600 mg. Bleeding usually occurred 48–96 h after the first tablet. When mifepristone was combined with gemeprost, half of a 1 mg vaginal pessary was inserted into the vagina 48 h after the dose of mifepristone.

In all these studies the women were followed up at 1, 2 and 4 weeks after the treatment and an assessment of the success rate, complications, morbidity and in some cases blood loss was made. ‘Complete’ abortion was deemed to have occurred if by 4 weeks the concentration of hCG in blood had fallen to below 50 mIU/ml, the uterus had returned to non-pregnant size, vaginal bleeding had ceased and the cervix was closed. ‘Incomplete’ abortion was defined as retained products of conception in the absence of fetal heart on ultrasound but continued vaginal bleeding or hCG concentrations which failed to fall by 4 weeks. ‘Failure’ was defined as an ongoing pregnancy (fetal heart present and rising levels of hCG) even although bleeding had been induced by the treatment.

In a minority of women blood loss was assessed objectively during induction of abortion and in the next few days by collecting all the soiled pads and measuring alkaline haematin by the method of Hallberg & Nilsson (1964).
Results

Table 1 compares the efficacy of the surgical and medical means of inducing abortion. Vacuum aspiration is a highly effective means of inducing therapeutic abortion although a small percentage (~5%) of women required further evacuation due to retained products. When gemeprost pessaries alone were used the efficacy was similar although there were 2 ongoing pregnancies. However, in agreement with larger series, mifepristone alone at a dose of 600 mg induced complete abortion in only 60% of women although some bleeding was induced in all but one woman (Odland & Birgerson, 1987). However, when mifepristone was followed 48 h later by a single gemeprost pessary the efficacy was similar to that of vacuum aspiration. There were no ongoing pregnancies in this group. In these studies the dose of gemeprost (0.5–1 mg) was one fifth that required when gemeprost pessaries alone were used (4–5 mg). As a result the incidence of prostaglandin-induced side effects (diarrhoea and abdominal pain) was reduced but not abolished (Table 2).

**Table 1. Comparison of surgical versus medical induction of abortion ≤42 days (≤56 days amenorrhoea) in women**

<table>
<thead>
<tr>
<th></th>
<th>Complete (%)</th>
<th>Incomplete (%)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuum aspiration</td>
<td>86 82 (96.5)</td>
<td>3 (3.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gemeprost</td>
<td>61 55 (91)</td>
<td>4 (6.5)</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>20 12 (60)</td>
<td>3 (15)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Mifepristone + gemeprost</td>
<td>100 95 (95)</td>
<td>5 (5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>


**Table 2. Side effects associated with induction of therapeutic abortion (pregnancy ≤42 days) in women**

<table>
<thead>
<tr>
<th></th>
<th>Vomiting (%)</th>
<th>Diarrhoea (%)</th>
<th>Pain* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemeprost</td>
<td>61 21 (34)</td>
<td>26* (43)</td>
<td>26* (43)</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>20 4 (20)</td>
<td>2* (10)</td>
<td>0* (0)</td>
</tr>
<tr>
<td>Mifepristone + gemeprost</td>
<td>100 38 (38)</td>
<td>15* (15)</td>
<td>10* (10)</td>
</tr>
</tbody>
</table>

*Requiring opiates. Values with different superscript are significantly different, P < 0.001 (\(2^\text{a}\) test).

There were no significant differences between the 3 doses of mifepristone although 3 of the 5 incomplete abortions occurred in the 400 mg group. The single woman in the 500 mg group who required surgical intervention had pain and bleeding 5 h after being given the gemeprost pessary. Under anaesthesia the products of conception were removed from the cervical os with minimal bleeding. As we gained experience it was found that it was often possible to remove the products of conception from the vagina about 3 h after inserting the vaginal pessary. In retrospect emergency evacuation under general anaesthesia was probably unnecessary in this woman.
As the efficacy of the gemeprost alone or in combination with mifepristone is comparable to that of vacuum aspiration, the acceptability is determined by the side effects. Vomiting was relatively common in all groups (20–38%) but it should be remembered that nausea and vomiting are very common in early pregnancy and may have occurred independent of the therapy (Cameron & Baird, 1988). The incidence of diarrhoea and lower abdominal pain requiring opiate analgesia was higher in those women given gemeprost alone than in the combination group (Table 2). The assessment of pain and hence requirement for analgesia is difficult to determine objectively, but it appears that a higher percentage of those receiving gemeprost alone (and hence a larger dose of prostaglandin) requested relief of pain. Pretreatment with mifepristone therefore lowered the dose of gemeprost required to evacuate the uterus.

After termination of pregnancy vaginal bleeding occurred for about 10–14 days in the majority of women (Table 3). The duration of vaginal bleeding was significantly shorter following vacuum aspiration than after medical termination. The total blood loss, including that at termination, was similar in all the groups and the median value (73 ml, range 13–398 ml) was equivalent to a heavy menstrual period. In no woman was the bleeding so heavy that she required blood transfusion and the drop in mean haemoglobin concentration was clinically insignificant.

<p>| Table 3. Duration and amount of bleeding after termination of pregnancy of &lt;42 days in women |
|---------------------------------|----------|--------|----------|</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Duration (days)</th>
<th>No.</th>
<th>Amount (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemeprost</td>
<td>60</td>
<td>10·9 ± 0·7</td>
<td>29</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>19</td>
<td>12·8 ± 1·9</td>
<td>4</td>
</tr>
<tr>
<td>Mifepristone + gemeprost</td>
<td>95</td>
<td>13·8 ± 0·8</td>
<td>57</td>
</tr>
<tr>
<td>Vacuum aspiration</td>
<td>58</td>
<td>10·0 ± 1·1</td>
<td>39</td>
</tr>
<tr>
<td>Values are mean ± s.e.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No women in the groups treated with mifepristone in combination with gemeprost required re-admission to hospital because of clinical evidence of pelvic infection, although 7% of women received antibiotics prophylactically because of pathogenic organisms (β-haemolytic streptococcus, gonococcus, bacteroides etc.) in a routine vaginal swab.

The return of ovarian activity was followed in a minority of women after vacuum aspiration or gemeprost treatment. The urinary excretion of hCG, pregnanediol glucuronide and oestrone glucuronide was measured until the onset of the next menstrual cycle. There was no significant difference between the surgical and medical means of inducing abortion in the mean time of ovulation (Table 4) although the range was considerable. The delay to ovulation is directly related to regression of the corpus luteum as indicated by the decline in excretion of pregnanediol.

**Discussion**

These results demonstrate that a combination of pretreatment with the antigestagen (mifepristone) and a vaginal prostaglandin pessary (gemeprost) is a highly effective means of inducing abortion in early pregnancy (<42 days gestational age). Similar results have been obtained using a combination of mifepristone and a subtherapeutic dose of a 16-phenoxy-prostaglandin E-2 (sulprostone) by intramuscular injection (Bygdeman & Swahn, 1985; Swahn & Bygdeman, 1987). Mifepristone
sensitizes the uterus to the oxytocic action of prostaglandins probably by releasing endogenous prostaglandins from the decidua (Kelly et al., 1986). The dilatation of the cervix which occurs after 24 h is probably due to a similar mechanism. Thus a dose of prostaglandin which alone is ineffective induced contraction of the uterus and, in the majority of women, expulsion of the fetus. Mifepristone alone induced bleeding in the majority of women but without additional prostaglandin the incidence of ongoing pregnancies or incomplete abortion was unacceptably high at this stage of pregnancy. Even in earlier pregnancy (up to 24 days) 15 of 100 women given mifepristone alone required subsequent surgical evacuation of the uterus (Couzinet et al., 1986).

How do the complications and side effects of medical means of termination compare to vacuum aspiration? The blood loss is similar in all groups although bleeding lasts for slightly longer after medical termination. Pretreatment with antigestagen reduces the incidence of gastrointestinal side effects (diarrhoea and vomiting) of prostaglandins to acceptable levels. The majority of women experience pain during the abortion after administration of gemeprost. Rosén et al. (1979) found that when the abortifacient drugs were given at home the analgesic requirements were less than when they were given in hospital. It seems unlikely, however, that any medical means of induction of abortion will be totally free from pain and hence the side effects must be weighed against the slight risk and inconvenience of vacuum aspiration. The latter technique requires to be performed by skilled medical personnel if incomplete evacuations and side effects, e.g. uterine perforation and infection, are to be kept to a minimum.

Conclusions

Several promising potential methods for inducing abortion in early pregnancy are now available, although none has been developed which are sufficiently effective and free from side effects to be self administered on a wide scale without ready access to skilled medical help. Even the most effective regimen (combination of antigestagen and prostaglandin analogue) results in a small number of incomplete abortions (~5%) which require further treatment. Careful follow up is required to identify any ongoing pregnancies to prevent births of babies whose development may have been compromised. The accepted surgical methods also have a small but recognizable failure rate. It seems unlikely that the current methods could be used as a routine method of contraception or contragestation to be taken only in the event of suspected pregnancy. Even if the method was acceptable ethically and legally, the problems of synchronizing the ovarian and menstrual cycle remain (Baird & Cameron, 1985). However, the combination of an antigestagen and prostaglandin is a useful alternative to surgical evacuation and may have wide application in countries in which medical resources are in short supply.

We thank Sisters Michie, Hillier and Will for the management of the patients; Margaret Harper for typing the manuscript; and Roussel Laboratories Limited, for the mifepristone.
References


INDUCTION OF EARLY ABORTION WITH MIFEPRISTONE (RU486) AND TWO DIFFERENT DOSES OF PROSTAGLANDIN PESSARY (GEMEPROST)

MARY W RODGER, ALISON F LOGAN, DAVID T BAIRD

UNIVERSITY OF EDINBURGH, DEPARTMENT OF OBSTETRICS & GYNAECOLOGY, CENTRE FOR REPRODUCTIVE BIOLOGY, 37 CHALMERS STREET, EDINBURGH EH3 9EW U.K.

ABSTRACT

One-hundred-and-twenty women of less than 56 days amenorrhoea were treated with a single dose of 600 mg of mifepristone in combination with half or a whole 1 mg gemeprost vaginal pessary. Complete abortion was induced in 119 (99%) women and there were no continuing pregnancies. There were few gastro-intestinal side effects following prostaglandin. The smaller dose of prostaglandin caused significantly less severe pain. This study confirmed the effectiveness of mifepristone and prostaglandin for the induction of early abortion but suggests that more research should be carried out to determine the lowest effective doses of both drugs.

INTRODUCTION

The majority of therapeutic abortions in the UK are performed in the first 12 weeks of pregnancy when it is relatively easy to surgically evacuate the uterus by vacuum aspiration (1). Although vacuum aspiration is a safe procedure, skilled medical and nursing personnel are required as well as, in many cases, a general anaesthetic. The risk of vacuum aspiration increases by 15-30% for every week of delay after 8 weeks of amenorrhoea (2) and hence a method of inducing abortion medically in early pregnancy would be very useful.

Although the application of any method of medical termination of pregnancy is determined primarily by its effectiveness in the induction of complete abortion, another important consideration is its acceptability. Rosen et al. have shown that the acceptability of an abortion method is related to the incidence of side effects that it causes (3). For medical termination to be a practical alternative to vacuum aspiration it must, therefore, have a comparable rate of complete abortion in addition to causing few side effects. Although prostaglandin analogues of the E series will induce complete abortion in around 90% of women of less than 7 weeks amenorrhoea, about 50% of women experience vomiting, diarrhoea or moderate to severe pain (4). The antigestagen mifepristone (RU 486) causes fewer side effects than prostaglandin. However, the incidence of incomplete abortion is unacceptably high and increases markedly with gestation (5,6).

We have previously demonstrated the effectiveness of a combination of mifepristone with prostaglandin by adding a subtherapeutic dose of prostaglandin pessary to treatment with a single dose of mifepristone. Complete abortion can be induced in 95% of women of less than 8 weeks amenorrhoea with few side effects, in particular little pain (7).

In this present trial we have studied not only the efficacy but also the side effects of treatment with a single dose of mifepristone in combination with 2 different doses of gemeprost (Cervagem) pessary.

PATIENTS AND METHODS

Local general practitioners and family planning centres were asked to refer women of less than 56 days (8 weeks) amenorrhoea to the Gynaecological Out-Patient Department of the Royal Infirmary of Edinburgh. One-hundred-and-twenty women with grounds for termination of pregnancy under the provision of the 1967 Abortion Act were recruited for the study. All women were aged over 18 years and had no history of serious medical disorders, complicated pregnancies or evidence of threatened abortion. Local Ethical Committee approval was granted for the trial and written informed consent obtained from each woman prior to treatment. The characteristics of the women treated are shown in Table I.

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Table I. Patient Characteristics

<table>
<thead>
<tr>
<th>Non-Randomised</th>
<th>Group</th>
<th>Randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 Pessary n=30</td>
<td>1 Pessary n=30</td>
<td>1/2 Pessary n=30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.1±1.1</td>
<td>26.6±1.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.5±1.2</td>
<td>164.7±1.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.5±1.2</td>
<td>60.0±1.6</td>
</tr>
<tr>
<td>Gestation (days)</td>
<td>48.8±0.6</td>
<td>48.7±1.0</td>
</tr>
<tr>
<td>Parous (%)</td>
<td>13 (43%)</td>
<td>8 (27%)</td>
</tr>
</tbody>
</table>

The data show mean ± standard error of mean save for parity which is presented as the number of parous women (%).

Pregnancy was confirmed by measurement of the plasma concentrations of hCG and gestational age was assessed by an accurate menstrual history, clinical examination and pelvic ultrasound scan. Blood was also taken for determination of the concentration of haemoglobin. All women were admitted to hospital on the first day of treatment and received a single oral dose of 600 mg of mifepristone. No dietary restrictions were imposed and women were asked to keep a daily record of any symptoms. Hourly records of temperature, blood pressure and pulse rate were made for 4 hours and the women were then allowed home.

Forty-eight hours after the administration of RU 486 the women were readmitted to hospital and treatment began with prostaglandin. The prostaglandin was gemeprost (Cervagel), a PGE₁ analogue, which is administered in vaginal pessary form - each pessary containing 1 mg of gemeprost in Witespol S-52 base. The first 30 women recruited to the study received one half of 1 mg gemeprost pessary. This was inserted into the posterior fornix of the vagina. The next 30 women received one whole 1 mg gemeprost pessary. The remaining 60 women were recruited to a double-blind randomised trial of a half or one whole 1 mg gemeprost pessary. The prostaglandin was administered by a member of staff who was not involved in the study and who played no subsequent part in the management of the patient. In this way neither the patients nor the investigators knew the dose of gemeprost given.

The women remained supine for at least 1 hour following prostaglandin administration. Hourly observations of temperature, blood pressure and pulse rate were made for 4 hours. Prophylactic medication was not prescribed. However, analgesia was given as required. Oral paracetamol (1g) was given for mild pain, dihydrocodeine (30 mg) for moderate pain and intramuscular diamorphine (5 mg) for severe pain. No dietary restrictions were imposed and the women were discharged home once pelvic pain and vaginal bleeding had settled. The women were reviewed on 3 occasions, the follow-up visits being performed one, two and four weeks following treatment. At each visit a vaginal examination was performed to assess the state of the cervix and uterine size and blood was taken for estimation of the concentration of hCG and haemoglobin. Abortion was considered complete if by four weeks vaginal bleeding had ceased, the cervix was closed, the uterus normal sized and the plasma concentration of hCG was less than 200 mIU/l. The women were discharged from our care following the onset of their next menstrual period.

hCG was assayed using commercial reagents (Serono, UK), the lower limit of sensitivity of the assay being 3mIU/ml plasma. Statistical analysis was by the Mann-Whitney U test, the t test for independent samples and χ² test (with Yates correction where appropriate). The data are presented as median (range) or mean ± standard error of the mean.

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RESULTS

One-hundred-and-nineteen (99%) of the 120 women treated aborted completely. There were no continuing pregnancies and only one woman, randomised to the group receiving a half pessary, required surgical intervention (Table II). This primigravida was 53 days from her last menstrual period when treated. She was taken to theatre 8 hours following prostaglandin administration because of heavy vaginal bleeding which continued despite the administration of further prostaglandin. In theatre the gestational sac was found to have incompletely separated and surgical evacuation of the uterus was performed. Her haemoglobin fell from 11.5 g/dl to 8.5 g/dl and she received a two-unit transfusion of red cell concentrate.

One woman randomised to the group receiving a whole pessary aborted 36 hours after mifepristone - prior to prostaglandin - and has, therefore, been excluded from the analysis of side effects subsequent to prostaglandin. There were found to be no statistically significant differences between the four treatment groups in terms of physical characteristics and parity. Detailed statistical analysis and comparison of the four groups in terms of onset of bleeding and pain, duration of bleeding, interval to the next period, time of passage of products of conception and use of analgesics was made. Again, no statistically significant differences were found and therefore the following data have been pooled and will be presented as Group I which consists of the 60 women who were given a half pessary and Group II which consists of the 59 women who received a whole pessary.

Bleeding was induced in all women treated. The median (range) onset of bleeding was 33.1 (23.8, 53.7) hours following mifepristone in Group I and 36.4 (12.3, 53.2) hours following mifepristone in Group II. Bleeding continued for 13.5 (3, 35) days following treatment in Group I compared with 12.5 (3.44) days in Group II. Although there was not a significant drop in the concentration of haemoglobin following treatment in Group I, there was a small though statistically significant fall in Group II. Only one woman (in Group I) required blood transfusion. The median interval to the next menstrual period was 32.5 (16, 49) days in Group I and 32.5 (16, 60) days in Group II (Table III).

Table II Incidence of Abortion

<table>
<thead>
<tr>
<th></th>
<th>Non-Randomised</th>
<th>Randomised</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/2 Pessary n=30</td>
<td>1 Pessary n=30</td>
<td>1/2 Pessary n=30</td>
</tr>
<tr>
<td>Complete Abortion</td>
<td>30 (100%)</td>
<td>30 (100%)</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Incomplete Abortion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (3%)+</td>
</tr>
<tr>
<td>Continuing Pregnancy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

+ required surgical evacuation of uterus for heavy vaginal bleeding eight hours following gemeprost.

* one woman aborted 36 hours following RU 486.
Table III. Bleeding following Therapeutic Abortion

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Onset of Bleeding after mifepristone (hours)</th>
<th>Duration of bleeding (days)</th>
<th>Haemoglobin before treatment (g/dl)</th>
<th>Haemoglobin after treatment (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (1/2 Pessary)</td>
<td>33.1 (23.8, 53.7)</td>
<td>13.5 (3.35)</td>
<td>13.0 (10.2, 14.6)</td>
<td>12.8 (8.5, 14.6)</td>
</tr>
<tr>
<td>II (1 Pessary)</td>
<td>36.4 (2.3, 53.2)</td>
<td>12.5 (3.34)</td>
<td>12.9 (11.0, 15.4)</td>
<td>12.5 (9.0, 14.4)*</td>
</tr>
</tbody>
</table>

The data show median (range)

\*p = 0.0142 (u=1214).

Not all women experienced pelvic pain. Of the 59 women in Group I who reported pelvic discomfort the median (range) onset was 31.9 (3.52.6) hours after mifepristone compared with 33.0 (5.5, 51.5) hours in the 56 women in Group II. Although pelvic pain was commonly reported prior to prostaglandin administration, only one woman used analgesia during this 48 hours, taking a single oral 1g dose of paracetamol for mild dysmenorrhealike discomfort.

Following prostaglandin administration, significantly fewer women in Group I experienced severe pain. Only 6 (10%) women in Group I compared with 17 (29%) women in Group II requested opiate analgesia. Otherwise the use of analgesia was similar in both groups with 27 (45%) women in Group I and 19 (32%) women in Group II requesting no analgesia at all (Table IV).

Table IV. Analgesia during Therapeutic Abortion

<table>
<thead>
<tr>
<th>GROUP</th>
<th>I (1/2 Pessary)</th>
<th>II (1 Pessary)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=60</td>
<td>n=59</td>
<td>n=119</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>6 (10%)*</td>
<td>17 (29%)</td>
<td>23 (19%)</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>6 (10%)</td>
<td>6 (10%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>21 (35%)</td>
<td>17 (29%)</td>
<td>38 (32%)</td>
</tr>
<tr>
<td>Nil</td>
<td>27 (45%)</td>
<td>19 (32%)</td>
<td>46 (39%)</td>
</tr>
</tbody>
</table>

\* P < 0.05, \( \chi^2 = 5.378, \) DF=1.

The products of conception were identified during the treatment of 48 (80%) women in Group I 3.7 (2.3, 6.4) hours following gemeprost administration and during the treatment of 55 (92%) women in Group II 3.7 (1.8, 9.8) hours after gemeprost. There were few gastrointestinal side effects in either Group I or Group II. As expected, the incidence of nausea was high in both groups prior to treatment (Group I 41 (68%) women, Group II 42 (70%) women). However, the incidence of nausea fell in both groups during treatment (Group I 25 (42%) women, Group II 30 (51%) women).
The incidence of vomiting and diarrhoea was not significantly increased during treatment in either group.

The plasma concentration of hCG fell dramatically over the first 7 days following treatment (Table V). However, it is of note that hCG was still detectable two and four weeks following treatment.

Table V. Plasma Concentration of hCG Before and After Treatment

<table>
<thead>
<tr>
<th>hCG (mIU/ml)</th>
<th>Recruitment</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1/2 Pessary)</td>
<td>34465</td>
<td>762</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>(841,249900)</td>
<td></td>
<td>(13,12160)</td>
<td>(&lt;3, 4937)</td>
<td>(&lt;3, 426)</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 Pessary)</td>
<td>46020</td>
<td>919</td>
<td>138</td>
<td>7</td>
</tr>
<tr>
<td>(313,255000)</td>
<td></td>
<td>(5,8286)</td>
<td>(&lt;3,3811)</td>
<td>(&lt;3,372)</td>
</tr>
</tbody>
</table>

DISCUSSION

This study confirms our previous findings that a single dose of mifepristone used in combination with a small dose of gemeprost effectively induces complete abortion before 8 weeks of amenorrhoea (7). Abortion was induced in all women treated in the study with only one woman requiring surgical intervention. There were no continuing pregnancies. Although there was no difference in the outcome of treatment when a whole as opposed to a half pessary was used, there was a significant decrease in the incidence of severe pain when the smaller dose of prostaglandin was given. Even when a half pessary was used, however, 10% of women still requested opiate analgesia. This finding is in keeping with our own previous findings (7) and those of Bygdeman & Swahn (8) (who used a comparable dose of Sulprostone, a PGF2 analogue) and suggests that perhaps a 4-hour stay in hospital after prostaglandin administration is preferable. Such a stay in hospital would have the further advantage of confirmation of abortion - the majority of women will pass products of conception during this 4 hours. The duration of bleeding following treatment was similar to the duration of bleeding after vacuum aspiration or medical abortion using prostaglandin (9). However, some women continued to spot until the onset of their next menstrual period.

The level of hCG was slow to fall after an initial large drop during the first week following treatment. This is due in part to the long half-life of hCG in plasma but also perhaps to the presence of a small amount of residual trophoblast after abortion.

With the recent granting of a product licence in France, the use of mifepristone and prostaglandin for the induction of early abortion will undoubtedly become widespread. Although many of the restrictions and requirements of its use under research conditions will be unnecessary, there are several that should remain mandatory. It is important that an intrauterine pregnancy be established prior to treatment as mifepristone seems ineffective in the disruption of ectopic pregnancy (10). Hospital admission (though not necessarily to a bed) for four hours following prostaglandin administration is advisable. Careful follow-up is essential following treatment to exclude the presence of a continuing pregnancy. One visit would probably suffice and the most appropriate time would be 4 weeks following treatment.

Six-hundred mg of mifepristone used in combination with a half 1 mg gemeprost pessary is highly effective in the induction of early abortion. It causes very few side effects - in particular, it does not increase the incidence of vomiting and diarrhoea and it causes little pain. Hopefully, this combination of antigestagen and prostaglandin will soon become much more widely available as an alternative to vacuum aspiration. In the meantime some fine tuning of the dose regimen, in particular the dose of prostaglandin used, is required, as the minimum effective dose of RU 486 and prostaglandin is not yet known.
ACKNOWLEDGEMENTS

We are grateful to Sister H Hillier and the nursing staff of Ward 54 of the Simpson Memorial Maternity Pavilion for their help with patient care. We would like to thank the staff of the Reproductive Endocrine Laboratories, Centre for Reproductive Biology, for performing the hCG assay and Margaret Harper for typing the manuscript. The mifepristone was kindly supplied by Ms Angela Davy of Roussel Laboratories Limited.

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BLOOD LOSS FOLLOWING INDUCTION OF EARLY ABORTION USING MIFEPRISTONE (RU 486) AND A PROSTAGLANDIN ANALOGUE (GEMEPROST)

MARY W RODGER and DAVID T BAIRD
University of Edinburgh, Department of Obstetrics & Gynaecology
Centre for Reproductive Biology, 37 Chalmers Street
Edinburgh EH3 9EW - UK

ABSTRACT

The pattern and amount of blood loss following induction of therapeutic abortion using mifepristone (RU 486) and a prostaglandin E analogue (gemeprost) was studied in 222 women of less than 63 days amenorrhoea. A single oral dose of mifepristone (400, 500 or 600 mg) was followed 48 hours later by a half or 1 mg gemeprost vaginal pessary. Complete abortion occurred in 218 (98%) women without necessity for surgical evacuation of the uterus. Bleeding commonly occurred following administration of mifepristone and prior to prostaglandin administration. The median duration of bleeding following abortion was 13 days with a range of from 1 to 44 days. There was a wide individual variation in measured blood loss between women, from 14 to 512 ml, with a median loss of 74 ml. The amount of blood loss was independent of the dose of mifepristone or prostaglandin but was significantly correlated with gestation. These results confirm that the combination of mifepristone and gemeprost is a highly effective and safe method of inducing therapeutic abortion medically. As the amount of blood loss increases with increasing gestation, it is suggested that its use should be restricted to women with amenorrhoea ≤ 56 days.

Correspondence and reprint requests to: D.T. Baird.

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INTRODUCTION

In spite of the safety and efficacy of termination of pregnancy in the first 12 weeks by vacuum aspiration of the uterus, non-surgical methods would be potentially less expensive and more convenient. Analogue of prostaglandins administered either intramuscularly or by vaginal pessary induce complete abortion in over 90% of women in the first 8 weeks of pregnancy but their widespread acceptance is limited by the high incidence of side effects (1). Recently, it has been demonstrated that the side-effects can be reduced to a minimum with a much reduced dose of prostaglandin and efficacy maintained if the woman is pretreated with mifepristone (RU 486) (2, 3). This antigestagen antagonises the effect of progesterone on the uterus and induces a marked increase in the sensitivity to exogenous prostaglandins. Two recent reports have demonstrated that the combination of mifepristone given as a single oral dose of 600 mg followed 48 hours later by 1 mg gemeprost pessary will induce complete abortion in over 95% of women of less than 56 days amenorrhoea (4,5).

If such a method of medical abortion is to be applied outside the context of a clinical trial it must be demonstrated that the method is not only effective but safe. Of particular concern is the potential danger of excessive uterine bleeding either as an acute episode during the passage of the fetus and placenta or due to continued loss over several weeks. Conventional gynecological teaching dictates that incomplete abortions should be treated by surgical evacuation although many spontaneous abortions in the early weeks of pregnancy resolve without surgical intervention. Previous studies have demonstrated that although the bleeding following medical termination with prostaglandins alone persists for longer than following vacuum aspiration, the total measured blood loss was similar (6). Preliminary data in a few women in whom abortion was induced with mifepristone alone or in combination with gemeprost showed highly variable loss ranging from 2 to 227 ml (3,7). In this study we have recorded the pattern of bleeding in 222 women following induction of abortion with mifepristone and gemeprost. In addition the total blood loss was measured by a quantitative method.

PATIENTS AND METHODS

222 women undergoing medical termination of pregnancy, were asked to collect all soiled sanitary wear in order that an objective measure of blood loss could be made using a modification of the alkaline haematin method described by Hallberg and Nilsson (6). All women were less than 63 days from their last menstrual period with uncomplicated, intrauterine pregnancies. When there was doubt about the menstrual history, the gestational age was confirmed by pelvic ultrasound scan using a 7.5MHz vaginal probe. All women had grounds for termination of pregnancy under the provision of the 1967 Abortion Act. Local Ethical Committee approval was granted for the trial and written informed consent obtained from each patient prior to treatment. Abortion was induced using a combination of the antiprogestrone mifepristone \(^*\) and the prostaglandin E analogue gemeprost \(^**\). A single dose of 400 mg, 500 mg or

\[\text{RU-486} - \text{Roussel Laboratories Limited, Broadwater Park, North Orbital Road, Denham, Uxbridge, Middlesex, UB9 5HP, U.K.}\]

\[\text{Gemeprost} - \text{May & Baker Limited, Ranham Road South, Dagenham, Essex, RM10 7XS, U.K.}\]
600 mg of mifepristone was administered orally on the first day of treatment with either a half or a whole 1 mg gemeprost pessary being inserted into the posterior fornix of the vagina 48 hours later. Details of treatment and outcome are given briefly in Table I and have been previously reported (4,9). There were no significant differences between the four groups in terms of height, weight, gestation, parity, onset of bleeding following mifepristone or duration of bleeding following abortion.

### Table I. Incidence of abortion and pad collection after administration of mifepristone followed by cervagem 48 hours later

<table>
<thead>
<tr>
<th>Gestation (days)</th>
<th>Dose of mifepristone</th>
<th>n</th>
<th>Dose of gemeprost 1 pessary</th>
<th>1/2 pessary</th>
<th>Complete abortion n (%)</th>
<th>Complete pad collection n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 56</td>
<td>400</td>
<td>33</td>
<td>7</td>
<td>26</td>
<td>30 (91%)</td>
<td>30 (91%)</td>
</tr>
<tr>
<td>&lt; 56</td>
<td>500</td>
<td>12</td>
<td>2</td>
<td>10</td>
<td>12 (100%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>&lt; 56</td>
<td>600</td>
<td>164</td>
<td>101</td>
<td>61</td>
<td>163 (99%)</td>
<td>158 (96%)</td>
</tr>
<tr>
<td>&gt; 56 &lt; 63</td>
<td>600</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>13 (100%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>ALL</td>
<td>222</td>
<td>123</td>
<td>97</td>
<td>218</td>
<td>213 (96%)</td>
<td>213 (96%)</td>
</tr>
</tbody>
</table>

Women were instructed to record the pattern of bleeding on a daily menstrual record card and to collect all sanitary towels and tampons from the onset of bleeding following ingestion of mifepristone to the day when bleeding ceased. In addition, any blood passed during the abortion process in hospital was collected and added to the pooled sanitary towels.

Pads and tampons were added to a molar solution of sodium hydroxide and left to soak for 48 hours. A 1 ml sample of venous blood was taken at follow-up visit one week after abortion. This was added to 99 ml of molar sodium hydroxide and left for 24 hours. An aliquot of liquid from around the pads was taken and filtered and its optical density measured at 550 mm. The venous blood sample was treated in the same manner and the volume of blood calculated from the formula: Optical density of pads x volume of NaOH soaked in / Optical density of venous blood x 100 ml.

At recruitment and one week following abortion, blood was taken for estimation of the concentration of haemoglobin. 113 consecutive women underwent pelvic ultrasound on the day of prostaglandin administration. The gestational sac was measured in 3 dimensions and these measurements entered into the formula: \( \frac{4}{3} \pi r^3 \) from which the volume of the gestational sac was derived.

The data are expressed as median (range) because of the non-parametric distribution of data. The Mann-Whitney U test has been used for comparison. Pearson's correlation coefficients have been calculated between variables and a backward stepwise multiple regression has been carried out on several variables.
RESULTS

Abortion was complete in 218 of the 222 women in whom the combination of mifepristone and gemeprost was given. There were no ongoing pregnancies and three of the four failures who required surgical intervention were in the group given 400 mg mifepristone and have been reported previously (4). There was only one of the 177 women who were given 600 mg of mifepristone who required surgical evacuation as an emergency haemostatic measure (see below).

Nine women have been excluded from the analysis of blood loss; two women aborted following mifepristone but prior to administration of prostaglandin and in seven women the collection of pads was incomplete.

The first episode of bleeding occurred between 10 and 58 hours (median 35 hours) after the administration of the mifepristone. Although this bleeding was not measured separately in all women, it was reported subjectively as scanty or light and in no case was sufficient to cause concern. Several women had increased blood loss in the three hours following administration of gemeprost usually coinciding with the passage of the fetus. In one woman of 53 days amenorrhoea, this bleeding continued and surgical evacuation of the uterus was necessary as an emergency procedure 8 hours after administration of gemeprost. The haemoglobin concentration fell from 11.5 g/dl to 8.5 g/dl 24 hours after evacuation and two units of blood were transfused.

The duration and amount of bleeding varied considerably between individual women (Table II). Although the median duration of bleeding following prostaglandin was 13 days, the range was from 1 to 44 days. The concentration of haemoglobin fell by a small though statistically significant amount following treatment: from 13 (10.2, 15.6) g/dl at recruitment to 12.6 (8.5, 14.9) g/dl one week following treatment (p <0.001). In women of less than 56 days amenorrhoea, the amount of blood loss was not related to either the dose of mifepristone or gemeprost (Table II). The blood loss in women receiving a whole gemeprost pessary (75 (15,447) ml, n=109) was similar to that in women following a half pessary (70 (15,512) ml, n=51). The results for all doses of mifepristone and gemeprost were, therefore, pooled in the subsequent analysis.

Table II. Measured blood loss according to dose of mifepristone

<table>
<thead>
<tr>
<th>Dose of mifepristone (mg) (&lt; 56 days amenorrhoea)</th>
<th>n</th>
<th>Measured Blood Loss (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>30</td>
<td>71.5 (15, 339)</td>
</tr>
<tr>
<td>500</td>
<td>12</td>
<td>82.5 (19, 123)</td>
</tr>
<tr>
<td>600</td>
<td>158</td>
<td>70.0 (14, 512)</td>
</tr>
<tr>
<td>ALL</td>
<td>200</td>
<td>72.0 (14, 512)</td>
</tr>
</tbody>
</table>

Data show median (range).
Height, weight, gestational age, parity, change in haemoglobin concentration, measured blood loss, duration of bleeding and the volume of the gestational sac were studied further. Pearson's correlation coefficients were then calculated between each of the variables. The cube root of gestational sac volume previously listed was taken in order to reduce the wide variation in this variable and logarithmic (base 10) transformation was performed on the 213 blood loss measurements which were found not to be normally distributed.

Total blood loss increased with gestational age (Table III). Table IV shows the comparisons which had a correlation coefficient, r, greater than 0.25. Measured blood loss was significantly correlated with gestational age (Fig. 1), change in concentration of haemoglobin and gestational sac volume. Due to the relatively high correlation between gestational age and sac volume, both of these variables could not be included in the multiple regression analysis; gestational age was the variable allowed in the model.

Table III. Measured blood loss according to gestation

<table>
<thead>
<tr>
<th>Amenorrhoea (days)</th>
<th>n</th>
<th>Measured Blood Loss (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 35</td>
<td>3</td>
<td>31.0 (29, 31)</td>
</tr>
<tr>
<td>36 - 42</td>
<td>28</td>
<td>57.5 (14, 211)*</td>
</tr>
<tr>
<td>43 - 49</td>
<td>96</td>
<td>68.5 (15, 339)*</td>
</tr>
<tr>
<td>50 - 56</td>
<td>79</td>
<td>81.0 (19, 512)*</td>
</tr>
<tr>
<td>≥ 57</td>
<td>7</td>
<td>154.0 (84, 341)*</td>
</tr>
<tr>
<td>ALL</td>
<td>213</td>
<td>74.0 (14, 512)</td>
</tr>
</tbody>
</table>

* p <0.05; * p <0.0001; significance of difference from preceding value.

Data show median (range).

The backwards stepwise multiple regression, therefore, initially allowed for all the previously mentioned variables, with the exception of gestational sac volume. The model was reduced to include the effects of gestational age and change in haemoglobin concentration only, both variables were found to have highly significant effects (p <0.001) in the model.
Figure 1. Correlation between menstrual blood loss (MBL) and gestation.
\[ \log y = 10^{2.84} \times 46.98 \quad r=0.3 \]

Table IV. Correlation between blood loss and other variables in women receiving mifepristone

<table>
<thead>
<tr>
<th>Variables</th>
<th>( r )</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log10 blood loss v. gestational age</td>
<td>0.3</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Log10 blood loss v. gestational sac volume</td>
<td>0.3</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Log10 blood loss v. change in haemoglobin concentration</td>
<td>-0.43</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Gestational age v. gestational sac volume</td>
<td>0.71</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Weight v. height</td>
<td>0.3</td>
<td>( p &lt; 0.001 )</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This study has confirmed that a combination of a single dose of mifepristone followed by a gemeprost vaginal pessary 48 hours later is a highly effective method of inducing therapeutic abortion in early pregnancy. In the present study, 176 of 177 women given 600 mg mifepristone aborted completely following the prostaglandin. The fact that one woman required emergency surgical evacuation within hours of the administration of prostaglandin emphasises that ready access to skilled medical help is necessary. In contrast to previous reports the present publication included 13 women >56 days all of whom aborted completely without complication.
The majority of women started bleeding within 48 hours of taking the mifepristone before the administration of the prostaglandin. However, the bleeding was reported subjectively as being scanty and made no apparent difference to the clinical efficacy of the gemeprost vaginal pessary which was followed within 2 hours by increased abdominal pain and vaginal bleeding. The bleeding occurring with the passage of the fetus was often described as heavy although in many cases only amounted to less than 20 ml.

The total measured blood loss from administration of mifepristone to the cessation of bleeding some days after the passage of the fetus was within the same range as has been previously reported using RU 486 alone (3,7), gemeprost pessaries alone (6) and mifepristone in combination with gemeprost (3, 4). During vacuum aspiration under general or local anaesthesia, the measured blood loss is slightly higher than with medical abortion but because the duration of bleeding is less following abortion, the overall blood loss (76 ml) is similar (10). Although the mean menstrual blood loss is comparable to that of a heavy menstrual period (~80 ml), the amount is highly variable with women occasionally bleeding up to 500 ml.

The blood loss was unrelated to the dose of mifepristone or gemeprost. It has been suggested that the prostaglandin by causing the uterus to contract would prevent excessive blood loss. However, there is an increase in spontaneous uterine contractility in women given mifepristone (2) presumably due to release of endogenous prostaglandins by the decidua (11). In 6 women given only mifepristone, the median blood loss (62.45-227 ml) was similar to those given additional prostaglandin (3).

Although the combination was equally effective irrespective of gestation, the blood loss was significantly greater as the period of amenorrhoea increased. It is likely that as pregnancy advances and the fetus and placenta increases in size, there is a larger vascular area from which bleeding can occur. Moreover, retention of trophoblastic tissue is very common following both medical and surgical termination as indicated by the detection of hCG in serum for up to 4 weeks after abortion (4,12). The fact that the bleeding continues for up to 4 weeks after abortion in some cases is probably due to retention of trophoblast. hCG is detectable for some weeks following vacuum aspiration although the evacuation of the uterus is probably more extensive than following medical termination.

The blood loss in the 7 women >57 days amenorrhoea ranged between 84 and 341 ml. Although this quantity would not be life-threatening, it is sufficient to cause a decrease in haemoglobin concentration which could compromise the health of women in a population in which anaemia is endemic. From a practical point of view it is wise, therefore, to restrict medical termination using this method to <56 days amenorrhoea.
We are grateful to Nancy Evans for technical help; to Alison Logan and Heidih Hillier for nursing assistance; and to Dr Peter Thomas and Angela Davey at Roussel U.K. for statistical analysis and supply of mifepristone. Mary W Rodger was supported by a Fellowship from Roussel UK.

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Pretreatment with mifepristone (RU 486) reduces interval between prostaglandin administration and expulsion in second trimester abortion

MARY W. RODGER, DAVID T. BAIRD

Summary. The effect of pretreatment with mifepristone on prostaglandin-induced abortion was investigated in a double-blind randomized trial involving 100 women in the second trimester of pregnancy. The women were randomly allocated to receive either 600 mg oral mifepristone or placebo tablets 36 h before the administration of gemeprost pessaries. The median interval between administration of prostaglandin and abortion was significantly shorter in the mifepristone group (6-8 h) compared with the placebo group (15-8 h). The women pretreated with mifepristone required significantly fewer gemeprost pessaries to induce abortion and experienced significantly less pain than the women who had received placebo.

In 1987, 25% of abortions in England and Wales and 10% of abortions in Scotland were performed in the second trimester of pregnancy (Office of Population Censuses and Surveys 1987; Registrar General for Scotland 1987). Complications of abortion are related to the gestational age and the method used (Cates & Grimes 1981). It is therefore important that procedures for the induction of second trimester abortion minimize long- and short-term morbidity.

Since Karim & Filshie (1970) described the use of prostaglandins for termination of pregnancy, prostaglandins have been widely used to induce abortion. Local instillation techniques have been employed using extra- or intramniotic administration of naturally occurring prostaglandins, PGE₂ and PGF₂α. More recently, prostaglandin analogues have been used in the form of vaginal pessaries to induce abortion. Analogues of the PGE series, gemeprost (16, 16 dimethyl-trans Δ⁴-PGE₁, methyl ester) and meteneprost (9 methylene PGE₂) have the advantage of causing fewer gastrointestinal side-effects and less pain as well as having a cumulative abortion rate verging on 100% (Bygdeman et al. 1980; Cameron et al. 1987). Although the use of prostaglandins has greatly improved procedures for second trimester terminations, induction of abortion at this stage of pregnancy remains a long, distressing and painful experience. Despite improved cumulative abortion rates using prostaglandin analogues, about 20% of women will not have aborted after 24 h of treatment (Cameron & Baird 1984).

Mifepristone (RU 486) is a synthetic steroid which acts as an antigestagen, blocking progesterone receptors in target cells of the endometrium and myometrium. Mifepristone sensitizes the pregnant uterus to exogenous prostaglandin and we have shown previously that by adding a subtherapeutic dose of prostaglandin to treatment with a single dose of the antigestagen, complete abortion can be induced.
in 95% of women in the early first trimester (Rodger & Baird 1987). Preliminary results of a non-randomized study suggested that pretreatment with mifepristone in second trimester terminations significantly reduced the interval between extra-amniotic PGE2 instillation and expulsion as well as reducing the amount of prostaglandin required (Urquhart & Templeton 1987).

In this double-blind randomized placebo-controlled trial we have investigated whether pretreatment with a single 600-mg dose of mifepristone reduces the interval between administration of gemeprost pessaries and expulsion in women seeking termination of pregnancy between 12 and 18 weeks gestation.

**Subjects and methods**

A total of 100 women with uncomplicated pregnancies of between 12 and 18 weeks gestation were recruited to this study. All women were 16 years or older and had no serious medical disorders and were recruited after admission to the Simpson Memorial Maternity Pavilion. Before admission, all the women had been counselled by two doctors and found to have grounds for termination of pregnancy under the provision of the 1967 Abortion Act. Local ethics committee approval was granted for the study, and written informed consent was obtained from each woman before treatment, with parental or guardian consent where necessary.

Pregnancy was confirmed by measurement of urinary hCG, and gestational age was assessed by clinical examination and pelvic ultrasonography. Blood was taken to estimate haemoglobin before treatment.

After recruitment the women were allocated by random number table to receive three oral tablets of either 3×200 mg mifepristone (n = 50) or placebo (n = 50). No dietary restrictions were imposed and observation of temperature, blood pressure and pulse rate were made hourly for 4 h. During these 4 h an accurate record of any side-effects or symptoms was made.

After an interval of 36 h, the women were questioned closely about any symptoms, in particular about vaginal bleeding or pelvic pain, before the administration of gemeprost (Cervagel, May & Baker Ltd). A 1-mg gemeprost vaginal pessary was inserted into the posterior fornix and this treatment was repeated every 3 h until either abortion had occurred or a maximum of five pessaries had been given. If abortion had not occurred within 24 h of the first pessary a further course of up to five pessaries was given. Those women who had still not aborted 48 h after the insertion of the first pessary received an intravenous infusion of oxytocin supplemented, if necessary, by further gemeprost pessaries.

All women remained in bed throughout treatment with gemeprost. An intravenous infusion was sited before the insertion of the pessary and although oral fluids were allowed, solid foods were withheld. Temperature, blood pressure and pulse rate were measured every 3 h and any symptoms experienced were recorded. Prophylactic medication was not prescribed, but analgesia and anti-emetics were given as required: 7.5 mg of intramuscular diamorphine for pain and 50 mg of intramuscular cyclizine for vomiting. Intramuscular syntometrine (ergometrine maleate, 500 µg, and oxytocin, 5 iu, Sandon

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mifepristone group (n = 50)</th>
<th>Placebo group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>3 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>17 (34)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (34)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>13 (26)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10 (20)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (28)*</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (20)**</td>
<td>2 (4)***</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Faintness</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Indigestion</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* P<0.02, χ² = 5.488, d.f. = 1.
** P<0.05, χ² = 4.640, d.f. = 1.

Table 1. Characteristics in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone group (n = 50)</th>
<th>Placebo group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.5 (0-6)</td>
<td>21.9 (0-6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 (9-8)</td>
<td>161 (0-9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.9 (1-1)</td>
<td>60.5 (1-5)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>15.2 (0-2)</td>
<td>15.4 (0-2)</td>
</tr>
<tr>
<td>Parous (%)</td>
<td>17 (34%)</td>
<td>14 (28%)</td>
</tr>
</tbody>
</table>

Results are means (SE) values.
Mifepristone pretreatment for abortion

Table 3. Prostaglandin induction-to-abortion interval

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction-to-abortion interval (h)</td>
<td>6-8 (2-0-67-8)*</td>
<td>15-8 (5-9-95-6)*</td>
</tr>
<tr>
<td>Number of pessaries used</td>
<td>3 (1-10)**</td>
<td>5 (2-10)**</td>
</tr>
<tr>
<td>Injections of analgesia per woman</td>
<td>1-1 (0-1)†</td>
<td>1-5 (0-2)†</td>
</tr>
</tbody>
</table>

The data presented show median (range) except for analgesia which is presented as mean (SE).

* P<0-0001, U = 339.
** P<0-0001, U = 370.
† P<0-05, U = 975.

Products Ltd) was injected at expulsion. Unless the products of conception were deemed complete, surgical evacuation of the uterus was performed under general anaesthesia.

The women were allowed home after appropriate contraceptive counselling and were reviewed 4-6 weeks later. At the follow-up visit the women were asked about vaginal bleeding and any symptoms subsequent to the abortion. A vaginal examination was performed and a venous blood sample was taken for haemoglobin estimation. The women were discharged from our care after this visit if there were no problems.

Statistical analysis

The Mann–Whitney U-test and χ²-test have been used. The data are expressed as mean (SE) or median (range) values.

Results

There were no statistically significant differences in the characteristics of the women between the two groups (Table 1).

One woman who received her first gemeprost pessary 51 h after taking 600 mg of mifepristone has been excluded from the analysis of treatment outcome following prostaglandin because abortion was already well advanced.

Three women in the mifepristone group reported minimal spotting of blood from the vagina in the 36 h before prostaglandin treatment. Pelvic pain was a commonly reported symptom in both groups, with 17 (34%) women in the mifepristone group and 10 (20%) in the placebo group experiencing mild dysmenorrhoeic-like discomfort. Headaches were also common in both groups as was a feeling of tiredness, but significantly more women in the mifepristone group experienced both vomiting and nausea during this 36-h period than women in the placebo group (Table 2).

Pretreatment with mifepristone significantly decreased the interval between administration and abortion. The median (range) time interval to abortion after the insertion of the first gemeprost pessary was only 6-8 (2-0-67-8) h in the mifepristone group compared with 15-8 (5-9-95-6) h in the placebo group (P<0-0001).

Women who received the antigestagen required

Table 4. Frequency of incomplete abortion in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 49)</td>
<td>(n = 50)</td>
</tr>
<tr>
<td>Retained placenta</td>
<td>26 (53)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>Incomplete abortion</td>
<td>15 (31)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Complete abortion</td>
<td>8 (16)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Surgical evacuation of uterus</td>
<td>45 (92)</td>
<td>48 (96)</td>
</tr>
</tbody>
</table>

Fig. 1. Cumulative abortion rate. ◆, RU 486, n = 49; ○, placebo, n = 50.
significantly fewer gemeprost pessaries to induce abortion (median 3, range 1–10) than the women who received the placebo (median 5, range 2–10) (P<0.001). The requirement for analgesia was also significantly less in the mifepristone group. Following mifepristone in this group the mean number of injections of 7.5 mg diamorphine required per woman was 1.1 (SE 0.1) compared with 1.5 (SE 0.2) injections per woman in the placebo group (Table 3).

Of the 49 women available for analysis in the mifepristone group 43 (94%) aborted during or following the first course of pessaries (that is during the first 24 h of prostaglandin treatment), 2 (4%) women aborted after seven pessaries, and only one woman required supplementary oxytocin following two courses of pessaries to induce abortion. In the placebo group 40 (80%) aborted during the first 24 h of treatment, 4 (8%) required supplementary oxytocin, and 2 (4%) needed further prostaglandin in addition to oxytocin to induce abortion (Fig. 1).

There were no reported serious adverse reactions to gemeprost during treatment in either group. Only one woman (in the placebo group) required blood transfusion; she was given a 2-unit transfusion of red cell concentrate following an episode of heavy vaginal bleeding which occurred during surgical evacuation of the uterus.

The frequency of vomiting during prostaglandin treatment was similar in both groups, 20 (41%) women in the mifepristone group and 20 (40%) in the placebo group vomited. Although fewer women in the mifepristone group experienced diarrhoea (5 compared with 10 in the placebo group) this difference was not statistically significant.

There was a high rate of retained placenta and incomplete abortion in both groups and most women had surgical evacuation of the uterus, reflecting existing hospital practice (Table 4).

Overall, 43 (86%) women in the mifepristone group and 41 (82%) women in the placebo group returned for review. The median duration of bleeding following abortion was 12 (range 3–41) days in the mifepristone group and 14 (range 0–25) days in the placebo group. Five women in the mifepristone group and six in the placebo group were treated with antibiotics in the weeks between abortion and review because various pathogenic organisms were isolated from their endocervical swabs. Only one woman (in the mifepristone group) required hospital admission because of pelvic infection subsequent to retained products of conception.

Clamydia trachomatis was isolated from her swabs.

In both groups the concentration of haemoglobin had increased significantly following abortion.

Discussion

This double-blind randomized placebo-controlled trial of mifepristone or placebo treatment before prostaglandin-induced abortion has confirmed the preliminary findings by Urquhart & Templeton (1987). Pretreatment with mifepristone reduced the interval between prostaglandin administration and expulsion significantly and reduced the amount of prostaglandin required, leading to a much reduced need for opiate analgesia. There is evidence to suggest that mifepristone sensitizes the uterus to the oxytocic action of prostaglandins by releasing endogenous prostaglandins from the decidua (Bygdeman & Swahn 1985; Smith & Kelly 1987), and certainly this would explain both the reduced induction-to-abortion interval and small requirement for prostaglandin after priming with mifepristone.

Bygdeman & Christensen (1983) reported a shortening of the prostaglandin induction-to-abortion interval after a 12-h pretreatment with laminaria tent. The mean duration of labour in the second trimester induced by 16-phenoxypregel (sulprostone) or 15-methyl-PGF_{1α} was shortened to around 10 h after priming with laminaria, and over 90% of women aborted within 24 h of prostaglandin administration. However, the amount of prostaglandin required to induce abortion was higher than that required with mifepristone in our study, and subsequently the frequency of prostaglandin-related side-effects was also higher. Another obvious though practical consideration is the route of administration of the priming agent—much more skill is needed to insert the laminaria tent than to give mifepristone.

This combination of mifepristone pretreatment with vaginally administered gemeprost pessaries provides a simple, non-invasive and highly effective method of second trimester termination. Labour is dramatically shortened following the antigestagen, less prostaglandin is required and fewer women experience severe pain; this treatment regimen represents a vast improvement in terms of safety and acceptability.
Both mifepristone and prostaglandin analogues will induce softening and dilatation of the cervix in women at 7–11 weeks gestation (Radenstad et al. 1988). This softening which is associated with a change in the collagen and ground substance of the cervix, occurs physiologically in late pregnancy before the onset of labour. The length of labour and the occurrence of spontaneous delivery is directly related to the degree of cervical softening and dilatation before labour (Uldbjerg et al. 1983). Our findings suggest that priming of the uterus and cervix with mifepristone would have wide application in spontaneous and induced labour if it can be shown to be without hazard to the fetus.

Acknowledgments

We would like to thank Sisters Logan and Hillier and the nursing staff of Ward 54, Simpson Memorial Maternity Pavilion, for their invaluable help with patient management. The mifepristone and placebo were kindly supplied by Roussel Laboratories Ltd, Broadwater Park, North Orbital Road, Uxbridge, Middlesex UB9 3HP, UK, and we would like to thank Angela Davey of Roussel Laboratories for her help with the study design. The manuscript was kindly typed by Margaret Harper to whom we are most grateful.

References


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The efficacy and tolerance of mifepristone and prostaglandin in first trimester termination of pregnancy

UK MULTICENTRE TRIAL

Abstract

Objective—To investigate the use of oral mifepristone (RU 486) and vaginal gemeprost for the induction of legal first trimester abortion.

Design—An uncontrolled multicentre observational study.

Setting—13 Hospital gynaecological units in Scotland and England.

Subjects—588 Pregnant women with up to nine weeks amenorrhoea having legal abortions.

Interventions—Oral mifepristone 600 mg followed 48 h later by vaginal gemeprost 1 mg. Women stayed in the hospital for a minimum of 4 h on each occasion.

Main outcome measures—Frequency of complete abortion and the need for subsequent surgical evacuation, analgesia and blood transfusion.

Results—There was complete abortion in 94% (95% CI 92—96%). None of the 46 women at <43 days gestation needed surgical evacuation. This was performed in 6.5% of the remainder but among these the rate did not increase with gestation. Five women (four from one centre) required both curettage and blood transfusion. A fall in haemoglobin concentration of 2 g/dl occurred in only 1%. Narcotic analgesia was required after gemeprost by 37% of nullipara and 13% of multipara. Overall 26% had vomiting and 13% diarrhoea.

Conclusion—The sequential use of oral mifepristone and vaginal gemeprost is effective in inducing abortion up to the 63rd day of pregnancy. Efficient management of pain and bleeding is easier if women are in a hospital for some hours after the gemeprost.
thesis, and requiring skilled training. A number of attempts have been made to develop non surgical methods of early pregnancy termination, and these have usually involved prostaglandins or their analogues (Karim et al. 1977; Smith & Baird, 1980; Bygdeman, 1984; Cameron & Baird, 1988). In some studies complete abortion rates of 90% have been reported, but the use of prostaglandins has been limited by the occurrence of troublesome, particularly gastrointestinal, side effects.

Mifepristone (RU 486; 17 B-hydroxy-11B(4-dimethylaminophenyl)-17a(prop-1-ynyl)estro-4, 9-dien-3-one; Roussel Laboratories Ltd) is a potent antiprogestagen which, by its ability to block the action of progesterone on the pregnant uterus, provides another approach to drug induced termination of pregnancy. It is a synthetic nonsteroid which acts reversibly at the molecular level of receptor binding, having a high affinity for the progesterone receptor (Bauert, 1985). The drug also has antiglucocorticoid activity (Moguilewsky & Philipert, 1985), but clinical trials have not revealed signs and symptoms of adrenal insufficiency at doses required for its antiprogestagen activity (Spitz et al. 1989). There is also weak anti-androgenic (Philipert et al. 1985), but no anti-oestrogenic or antimineralocorticoid activity.

The success of mifepristone used alone in inducing abortion has been extremely variable but has never been more than 88% (Kovacs et al. 1984; Shoupe et al. 1986; Cameron et al. 1986; Couzinet et al. 1986; Editorial, 1987; Grimes et al. 1988) and its use has been complicated by occasional heavy bleeding (Couzinet et al. 1986; Editorial, 1987; Grimes et al. 1988; Bygdeman & Van Look, 1988). However, the combined use of mifepristone with a small dose of prostaglandin has proved much more effective and there are now a number of reports which testify to the efficacy of mifepristone used in combination with intramuscular sulprostone (PGE, analogue) (WHO. 1989) and intravaginal gemeprost (PGE, analogue) (Rodger & Baird, 1987; Dubois et al. 1988). These studies were restricted to gestations of seven and eight weeks respectively.

The purpose of this multicentre study was to assess the efficacy of mifepristone given in combination with gemeprost to terminate pregnancy of up to nine weeks gestation. The results presented are an interim analysis for a larger study of more than 1000 patients.

Subjects and methods

The study was an open, multicentre hospital investigation to assess the efficacy of mifepristone and vaginal prostaglandin in the termination of pregnancy up to nine weeks amenorrhoea. Women received a single oral 600 mg dose of mifepristone followed 48 h later by a 1 mg vaginal pessary of gemeprost (16,16-dimethyl-trans-D3-17a proglandin E1 methyl ester; May and Baker, UK). Women were reviewed over the course of the next four weeks to determine efficacy and tolerance. In each centre permission was obtained from the local ethics committee and termination of pregnancy was agreed under the conditions of 1967 Abortion Act. The intention was that all women would be at least 18 years old and of less than nine weeks gestation. There should have been no previous serious medical or psychiatric disorder, or treatment with glucocorticoid in the previous year. Gestation was assessed from the first day of the last menstrual period and by ultrasound, while viability was confirmed by human chorionic gonadotrophin (hCG) measurement and ultrasound.

Mifepristone tablets were taken in the presence of the investigators after base line data (demography and medical history) and consent had been obtained. All women remained in hospital for 4 h, during which time symptoms, pulse, temperature, blood pressure and blood loss were recorded, and then they were free to go. After 48 h they returned to hospital for assessment and for administration of the prostaglandin pessary. The women remained in hospital under observation for at least 4 h during which time general condition and signs and symptoms of abortion were assessed. Analgesic requirements were also noted. Women left the hospital when the investigators were satisfied that their clinical condition was stable but were requested to return for follow up 7, 14 and 28 days later, at which time efficacy and tolerance were further assessed by history and clinical examination. Women were free to visit the hospital doctor at any time between scheduled visits if necessary. Not all women attended for follow-up.

Results

Over a period of ten months until June 1988, 593 women were recruited from 13 centres (median number of women/centre 46, range 1–99). Two women withdrew after taking mifepristone, one
because she had changed her mind (the pregnancy continued to term and a normal baby was born), the other requested surgical termination. Two others vomited shortly after taking mifepristone tablets and were referred for surgical termination. A fifth had an ectopic pregnancy and, although she received mifepristone and gemeprost, eventually required laparotomy and is not therefore included in this analysis.

**Patient characteristics**

The median age was 24 years, and the range 16–45 years, with 75% in range 18–29 years. Although the intention was to restrict recruitment to women aged 18 years, five aged 16 or 17 were treated and have been included. The physical characteristics of the women are given in Table 1.

Of the 588 women, 206 (35%) had at least one previous vaginal delivery, and 130 (22%) had two or more, while 22 (4%) had had at least one caesarean section. One or more miscarriages had been experienced by 44 (7%) and at least 118 (20%) had had one previous termination.

The gestational age at the time of termination is given in Table 2: 70% of women were in the range 43–56 days. Fifteen pregnancies were of gestational age 64–69 days but were included in the analysis.

**Efficacy**

Of 588 women studied, 580 received the full regimen of mifepristone and gemeprost. Seven aborted with mifepristone alone and did not receive gemeprost for this reason. The eighth did not receive gemeprost, but was recorded as having aborted nine days after mifepristone.

Again of the 588 women, 553 (94.0%, 95% CI 92.1–96%) aborted completely without the need for a subsequent surgical procedure. Among the 35 women who had surgical evacuation of the uterus, six had this done around the time of gemeprost administration (four because of haemorrhage and two (one a twin pregnancy) because they did not abort after gemeprost). A further five had curettage following medical termination but before the first (7 day) follow-up, while in the interval 7–14 days a further eight had evacuation, and in the interval 15–28 days a further 13. Three women had evacuations beyond this period. The usual reason for subsequent evacuation of uterus was suspected retained products. This was usually suspected on clinical grounds but not always confirmed at the time of surgery. Ultrasound scans were not particularly helpful. Of 507 scans at the one week follow-up, 47 suggested retained products, but only nine of these women went on to have a surgical evacuation immediately or later.

Only nine women were lost to follow-up before the response could be fully determined. However, in six the investigator thought that abortion was complete before they left hospital (one had not required gemeprost), and two telephoned at the time of their next menstrual period. None of the nine was thought to have a continuing pregnancy, hence all nine were considered as successes.

It was necessary for 159 (27%) women to stay in hospital for longer than 4 hours after gemeprost administration, but most had been discharged by 8 hours. Fourteen (2%) remained for 9–48 hours.

None of the 46 women with gestation <42 days required surgery (Table 2). The rate of evacuation subsequent to this was between 6 and 7% and did not increase with advancing gestation.

**Bleeding**

Serious haemorrhage, requiring haemostatic curettage and blood transfusion occurred in five women, shortly after gemeprost administration in four and in the fifth during the subsequent few days. The women’s own assessment of bleeding

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the women in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Ponderal index</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Gestation length and number of women requiring surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age (days from LMP)</strong></td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>&lt;36</td>
</tr>
<tr>
<td>36–42</td>
</tr>
<tr>
<td>43–49</td>
</tr>
<tr>
<td>50–56</td>
</tr>
<tr>
<td>57–63</td>
</tr>
<tr>
<td>63–69</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
The major centres, considered other problems analgesia. However, there was a need for narcotic treatment, between nulliparous and parous women in the need for narcotic analgesia (37% compared with 13%). About 30% of both groups required non-narcotic analgesia. However, there was a considerable difference in narcotic use between the centres, the range being 8–50%.

Other problems

The major symptoms other than pain or bleeding were vomiting and diarrhoea (Table 7). One quarter of all women had vomiting during the 4 h after gemeprost administration while 13% had diarrhoea.

### Discussion

This large multicentre study shows that medically induced termination of pregnancy is a realistic alternative to surgery. Of 588 women, 94% had complete abortion induced without the need for surgical intervention. These results extend previous experience of the combination of mifepristone and prostaglandin both in terms of numbers and gestation. Using a dose of mifepristone 150 mg over four days followed by 1 mg pessary of gemeprost, Cameron & Baird (1988) reported successful abortion in 18 out of 19 women with 35–56 days amenorrhoea. Rodger & Baird (1987) studied 100 women of the same gestation who were given mifepristone 400–600 mg followed by gemeprost, and reported a 95% complete abortion rate. In a recent WHO multicentre trial (WHO, 1989) mifepristone 150–200 mg was given to 250 women with up to 49 days amenorrhoea before an intramuscular

### Table 3. Self-reported assessment of bleeding during and following treatment

<table>
<thead>
<tr>
<th>Women's assessment of bleeding</th>
<th>After mifepristone</th>
<th>After PG</th>
<th>Days following medical termination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–24 h</td>
<td>24–48 h</td>
<td>2 h</td>
</tr>
<tr>
<td>None</td>
<td>536 (91)</td>
<td>264 (45)</td>
<td>158 (27)</td>
</tr>
<tr>
<td>Light or spotting</td>
<td>30 (5)</td>
<td>181 (3)</td>
<td>225 (9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (2)</td>
<td>86 (15)</td>
<td>163 (28)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (0)</td>
<td>13 (6)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Excessive with clots</td>
<td>3 (0-5)</td>
<td>18 (3)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Information missing</td>
<td>6 (1)</td>
<td>6 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>588 (100)</td>
<td>588 (100)</td>
<td>580 (100)</td>
</tr>
</tbody>
</table>

The values are numbers of women with percentages in parenthesis. Not all women attended for follow-up after the procedure.

is given in Table 3. In 9% bleeding was described as severe or excessive in the 24–48 h period after mifepristone. A similar rate was reported 4 h after gemeprost. Two days after the procedure 16% noted severe or excessive bleeding but by nine days only 0-4%. Objective assessment of bleeding is given in Table 4 where differences in haemoglobin measurement immediately before treatment and seven days after gemeprost administration are reported (the five women who required blood transfusion were excluded). In 93% of the women there was little or no change (up to 1 g/dl), while in 1% of patients there was a decrease of 2-4 g/dl.

### Pain

The women's own assessment of pain is given in Table 5. Twelve (2%) reported severe pain after mifepristone administration and before gemeprost. Two hours after gemeprost administration, 21% reported severe pain but this had decreased to 10% by 4 h. By two days after the termination, 5% of women still complained of severe pain, but none by nine days. The objective assessment of pain is difficult but can be indirectly gauged by the need for analgesia (Table 6). Here there was a marked difference between nulliparous and parous women in the need for narcotic analgesia (37% compared with 13%). About 30% of both groups required non-narcotic analgesia. However, there was a considerable difference in narcotic use between the centres, the range being 8–50%.

### Table 4. Changes in haemoglobin in 521 women who had haemoglobin measured before treatment and 7 days after PG administration

<table>
<thead>
<tr>
<th>Change in Hb (g/dl)</th>
<th>Women n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase or no change</td>
<td>211 (40)</td>
</tr>
<tr>
<td>Decrease</td>
<td>276 (53)</td>
</tr>
<tr>
<td>0-1</td>
<td>28 (5)</td>
</tr>
<tr>
<td>1-2</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>3-4</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
injection of sulprostone. Overall 89% of women had a complete abortion, 7% were incomplete and 2% were treatment failures (the outcome could not be adequately determined in a further 2%). However, most of the curettings came from one centre and when this centre was excluded, the authors reported a 94% complete abortion rate, which was similar to a smaller single centre study using the same regimen (Bygdeman & Swahn, 1985). More recently Dubois et al. (1988) in France have reported a similar success rate.

The two major problems associated with medical termination of pregnancy are bleeding and pain. In the present study severe haemorrhage requiring blood transfusion occurred in five women (1%). This problem has been reported both in regimens which employ mifepristone alone (Kovaes et al. 1984; Cameron & Baird, 1988), and also in combined regimens (WHO, 1989). Subjective assessment of bleeding indicated that 9% of women had severe or excessive bleeding in the 24-48 h period following mifepristone administration and a similar proportion in the 4 h after gemeprost administration. After the procedure, 16% complained of severe or excessive bleeding at two days, but only 0-4% by nine days. However, objective assessment of blood loss by haemoglobin assessment was more reassuring, and other studies are also reassuring in this respect (Cameron & Baird, 1988; WHO, 1989). A measured blood loss of 72 ml (range 15-398 ml) has been reported in 72 women treated with the same regimen at up to 56 days amenorrhoea (Rodger & Baird, 1987). Further objective studies are required, while detailed acceptability studies should focus on this area. Dubois et al. (1988) have reported that the interval between mifepristone and prostaglandin can be reduced to 36 h without loss of efficacy, and this may reduce the occurrence of severe bleeding.

Pain was the other main problem (Tables 5 and 6). During gemeprost administration 28% of women required opiate analgesia. This is higher than other studies reporting combined regimens, 7-6% (WHO, 1989), 9% (Rodger & Baird, 1987), and 16% (Cameron & Baird, 1988), but is much less than with prostaglandin alone (Cameron & Baird, 1988). The reasons for this difference are not clear. However, the present study has highlighted the marked differences in analgesic requirement between nulliparous and parous women. Again there is scope for further study in this area and it might be anticipated that the circumstances of the abortion and

Table 6. Need for analgesia up to 4 h after administration of PG

<table>
<thead>
<tr>
<th>Analgesia</th>
<th>Nulliparous (n = 370)</th>
<th>Parous (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcoic</td>
<td>137 (37)</td>
<td>29 (13)</td>
</tr>
<tr>
<td>Non-narcoic</td>
<td>120 (32)</td>
<td>65 (30)</td>
</tr>
<tr>
<td>None</td>
<td>113 (31)</td>
<td>124 (57)</td>
</tr>
<tr>
<td>X^2 = 51.4, P&lt;0.005 (2 DF)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Appearance of new symptoms other than abdominal pain and vaginal bleeding

<table>
<thead>
<tr>
<th>Symptom</th>
<th>During 4 h after mifepristone (n = 588)</th>
<th>During 4 h after PG (n = 580)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (5)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (3)</td>
<td>150 (26)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (0-5)</td>
<td>73 (13)</td>
</tr>
</tbody>
</table>
the attitudes of the attendants might have a strong influence on the need for analgesia.

Other problems were infrequent, although 26% did complain of vomiting in the 4 h after gemeprost administration. The use of smaller doses of prostaglandin and, possibly, different analogues needs to be explored and will no doubt be addressed in future studies. Thus the efficacy and tolerance of medical as opposed to surgical termination of pregnancy is being increasingly defined. There is a need for more detailed studies of acceptability, but the initial response was very positive (Urquhart & Templeton, 1988), as was apparent in earlier studies of prostaglandin-only methods (Rosén et al. 1984). The implications of this development also extend to the organization of the health services. Clearly there will be a saving in operating theatre and anaesthesia time, but the procedure needs to be clinic based, and preferably hospital based, in view of the small but definite risk of severe haemorrhage. The appropriate facilities need to be developed and the most suitable environment will become evident with increased experience. It cannot be expected that in this country the advent of medical termination will increase access to termination, but the impact in the Third World could be considerable.

Acknowledgments

The original data were provided by Miss Angela Davey of Roussel Laboratories Ltd.

References


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Medical abortion in women of ≤56 days amenorrhoea: a comparison between gemeprost (a PGE₁ analogue) alone and mifepristone and gemeprost

J. E. NORMAN  
K. J. THONG  
M. W. RODGER  
D. T. BAIRD  
University of Edinburgh  
Department of Obstetrics and Gynaecology  
Centre for Reproductive Biology  
Chalmers St, Edinburgh EH3 9EW  
UK

The introduction of antiprogestrone, mifepristone, has increased interest in medical abortion and, in combination with a low dose of prostaglandin, appears to be a safe, effective method of early termination of pregnancy (Rodger & Baird 1987; Silvestre et al., 1990; UK Multicentre Trial 1990). The use of mifepristone allows a smaller dose of prostaglandin to be used than when using prostaglandin alone, resulting in fewer prostaglandin related side effects, and lower analgesic requirements. Whilst this is apparent from data on the two methods published separately, only one small study has directly compared mifepristone and prostaglandin with prostaglandin alone, and failed to find any difference in efficacy (Cameron & Baird 1988).

In this study, the effects of a new protocol for early termination of pregnancy (≤56 days amenorrhoea) using a low total dose of gemeprost, are reported. In addition, the efficacy and side effects of this method are compared with the use of mifepristone and gemeprost at the same gestation, collected as part of a World Health Organization multicentre trial, the manuscript of which is in preparation.

Subjects and methods

General practitioners and family planning clinics in the area were asked to refer pregnant women of ≤56 days amenorrhoea requesting abortion, and who had grounds for termination of pregnancy under the 1967 Abortion Act. Women were initially seen in the outpatient clinic, where a history was taken and a routine clinical examination performed. Once the decision to terminate the pregnancy was made, women who met the study
criteria were offered medical termination of pregnancy. Overall 201 women were recruited into the study, which was approved by the local reproductive medicine ethics subcommittee. Written informed consent was obtained from each woman before treatment.

The first 66 women (group 1) were recruited to receive gemeprost alone (1 mg every 6 h to a maximum of 3 mg), the next 63 women (group 2) were recruited to receive mifepristone and gemeprost (200-600 mg mifepristone followed 48 h later by 1 mg gemeprost). Thereafter, a further 170 women were randomized to receive either gemeprost alone (group 3) or mifepristone and gemeprost (group 4), in the dose regimens described above. Treatment was allocated by opening a sealed envelope containing directions to one or other protocol. The envelopes were prepared in advance so that an equal number of women were randomized to each group. Neither the woman, nor the investigator was blind to the treatment method. All women were aged over 16 years, and had had no serious medical disorders and no bleeding during this pregnancy. Women who had taken the oral contraceptive pill during the cycle before, or during, conception and women with a history of irregular menstrual cycles, were excluded from groups 2-4.

Treatment with gemeprost alone (groups 1 and 3)

Women were admitted to hospital on the first day of treatment (day 1). A pelvic ultrasound scan was performed to confirm the gestational age. Gestational sac diameter was recorded for subjects in group 3. Blood was taken for blood grouping, haemoglobin and serum human chorionic gonadotrophin (hCG) estimation and height and weight were recorded. The point prevalence of a series of common pregnancy or prostaglandin related symptoms was noted. A single gemeprost pessary (1 mg) was inserted into the posterior vaginal fornix. Women were instructed to remain in bed for the first hour after pessary insertion, and were then encouraged to mobilize or to sit up. Blood pressure, pulse rate and temperature were recorded every 3 h. The symptom questionnaire was repeated 6 h after the first pessary and, unless the woman had complained of severe abdominal pain, or abortion had occurred, a further 1 mg gemeprost was inserted into the posterior vaginal fornix. The process was repeated 6 h later and a third pessary was given, if necessary. The time at which bleeding and abdominal pain started and the number of episodes of vomiting and diarrhoea were noted. Analgesia was available as required: paracetamol, codeine and diatomphine were used in order for increasing severity of pain. Those who required a third prostaglandin pessary were encouraged to stay in hospital overnight. Blood was taken 24 h after prostaglandin administration for repeat measurement of the concentration of serum hCG.

Before discharge, anti-D was administered to rhesus negative women and a menstrual diary card was given to record the pattern of vaginal bleeding. Follow-up appointments were made for days 8, 15 and 29. Women were asked to use non-hormonal methods of contraception for the first post treatment cycle. Follow-up was extended until after the next menses for women in group 3.

Treatment with mifepristone and gemeprost (groups 2 and 4)

On the first day of treatment (day 1) an ultrasound scan was performed, and mean gestational sac diameter recorded. Blood was taken for blood grouping and haemoglobin and serum hCG estimation, and height and weight were recorded. A single dose of 200 mg, 400 mg or 600 mg mifepristone was given, the dose being determined by random allocation. Women were allowed home immediately after taking the tablets, and given a menstrual diary card to record the pattern of vaginal bleeding, and asked to use non-hormonal methods of contraception for the first menses after treatment. Follow-up was arranged for days 8, 15, and 43, until after the first menses.

Follow-up (all groups)

At the follow-up visit (day 8), the menstrual diary card was reviewed and any complications noted. A pelvic examination was performed. Blood was taken for measurement of serum hCG and haemoglobin. At the second follow-up examination (day 13) a similar protocol was employed. In addition, a pelvic ultrasound was performed. Those with an ongoing pregnancy (rising serum hCG, and a gestational sac of increasing diameter on pelvic ultrasound scan with or without an active fetal heart), underwent surgical uterine evacuation. Those few with an incomplete abortion (constant or slowly failing serum hCG and products of conception visible in the uterus on ultrasound scan) were managed conservatively or underwent surgical termination of pregnancy depending on their clinical condition. Four women given gemeprost alone were given a further pessary course, rather than undergoing surgical termination of pregnancy. Follow-up was attempted on all women until bleeding had ceased, and the duration of bleeding noted; those in groups 2-4 were followed up until menstruation had occurred, the interval from abortion to menstruation was noted and the women were asked how the whole bleeding episode compared with their normal menses.

Assays

Haemoglobin and serum hCG measurements were made by the local haematology and reproductive endocrine laboratories respectively.

Statistics

Continuous data were plotted before analysis to determine the distribution. Where the data were normally distributed, a transformation could be employed to achieve normality, the
Results
There were no significant differences between the groups on the first treatment day (Table 1). The effects of treatment in groups 1 and 3, and groups 2 and 4 were initially compared. There were no significant differences in results between the women who were randomly allocated to their treatment groups and those who were not, and therefore it was considered reasonable to combine the data on women in groups 1 and 3 to allow for more powerful comparisons with data on women in groups 2 and 4.

The full results of the comparisons between the group of women having the three doses of mifepristone will be published with the results of the Multicentre Trial, but there were no significant differences in abortion rate between the groups. Analytic requirements, duration of bleeding and all other outcome measures were the same in each mifepristone dose group. Of the 150 women treated with mifepristone and gemeprost 147 (98%) aborted completely without further intervention (Table 2). One woman (who had received 400 mg mifepristone followed 48 h later by 1 mg gemeprost) had an ongoing pregnancy after treatment; this was terminated surgically 3 weeks after mifepristone administration. Two other women had a haemostatic curettage: one (following 400 mg mifepristone) in another hospital 5 weeks after the start of treatment, and another (who had received 600 mg mifepristone) underwent sterilization and curettage at her request 8 weeks after the start of treatment. In neither did histological examination of the endometrial curettings show any trophoblastic material.

Of the 151 women treated with gemeprost alone, 132 (87.4%) aborted completely (Table 2). Nine women had an ongoing pregnancy after treatment and ten had evidence of an incomplete abortion. Four of the nine women with an ongoing pregnancy opted for a further course of pessaries, three subsequently aborted completely, and one required curettage. All other women with an ongoing pregnancy or incomplete abortion underwent uterine evacuation, bringing the total to 16. None required a haemostatic curettage. The combination of mifepristone and gemeprost was significantly more effective in inducing a complete abortion than gemeprost alone, with success rates of 98% and 87% respectively (P<0.0004 \( \chi^2 \)-test).

Analytic requirements were significantly greater in women treated with gemeprost alone than in those treated with mifepristone and gemeprost (P<0.0001, \( \chi^2 \)) (Table 3). There were no significant differences between the women treated with mifepristone alone and those treated with mifepristone and gemeprost for the following indices: duration of bleeding (mean 13.6 days vs 15.0 days, 95% CI 12.3 to 15.3; interval from induction of abortion to menstruation (mean 34.1 days vs 38.4 days, 95% CI 34.5 to 37.1); and change in haemoglobin concentration from day 1 to day 8 (median –0.4 g/dl vs range –1.6 to 1.0 g/dl, range –2.9 to 0.6 g/dl). There was a significant difference between the two groups for serum hCG on day 8, expressed as a percentage of the original value (median 17.8% range 0.5% to 277.0% vs median 3.57%, range 0.03 to 152.6%; P<0.0001). Since change in hCG and haemoglobin are critically dependent on the time after abortion, only data from women who attended for follow-up from day 7 to day 11 were included.

Of the 151 women treated with gemeprost alone, 117 completed the symptom questionnaire (Table 4). The first 24 women were treated as a pilot group; of the remaining 127 women to whom the questionnaire was applied, ten failed to fill in all the details. There was a significant increase in abdominal and pelvic pain following the first prostaglandin

Table 1. Characteristics of the women in each of the four groups on the first treatment day

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non randomized</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>(gemeprost alone)</td>
<td>(mifepristone and gemeprost)</td>
</tr>
<tr>
<td></td>
<td>(n=66)</td>
<td>(n=65)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26.2 (24.6 to 28.3)</td>
<td>26.9 (25.3 to 28.6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163±8 (162-165)</td>
<td>164±9 (163-166)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61±6 (57.8 to 65.0)</td>
<td>62±6 (59.9 to 64.5)</td>
</tr>
<tr>
<td>Amenorrhoea (days)</td>
<td>46±6 (45.0 to 47.8)</td>
<td>47±7 (46.4 to 49.0)</td>
</tr>
<tr>
<td>Parous women</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;28 weeks</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>&lt;28 weeks</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Gestational sac diameter (mm)</td>
<td>(not recorded)</td>
<td>19.5 (17.2 to 22.0)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12.9 (12.7 to 13.2)</td>
<td>13.2 (12.0 to 13.5)</td>
</tr>
<tr>
<td>hCG (IU/l)</td>
<td>28±50 (139 to 214 000)</td>
<td>47±720 (209 to 154 000)</td>
</tr>
</tbody>
</table>

Data are expressed as means (95% CI) except for parity (%) and medians (range) for serum human chorionic gonadotrophin (hCG) concentration. There were no significant differences between any of the four groups.
pessary in women treated with gemeprost alone, and a significant decrease in breast tenderness (Table 4). There was no change in the occurrence of headache, vomiting, indigestion, loss of appetite, constipation, faintness, tiredness, or dysuria following gemeprost.

The lower overall success rate of 87% in the group of women treated with gemeprost alone would preclude routine clinical use. To determine whether there were any factors which might predict outcome, characteristics of ‘successful patients’ (those who aborted completely after gemeprost without further intervention) and ‘unsuccessful patients’ (those who failed to abort completely after gemeprost) were compared (Table 5). The median (range) number of episodes of vomiting and diarrhoea were 0 (0–5) and 0 (0–6) in the group who aborted completely following gemeprost, and 0 (0–3) and 0 (0–4) in the group who failed to abort (ns).

Women who aborted completely following treatment bled a median (range) time of 300 minutes (90–720) after the first prostaglandin pessary, significantly earlier than those who failed to abort, at 360 minutes (165–765) after gemeprost (P<0.05). Abdominal pain occurred at a median (range) of 195 (20–540) minutes after the first pessary in those in whom the procedure was successful, compared to 180 (110–420) minutes after the first pessary in those who did not abort (ns). Those who aborted following treatment had a significantly greater requirement for analgesia than those who failed to abort (P<0.003); 58% of the ‘unsuccessful’ required no analgesia compared to 19% of the ‘successful’ treatments.

Discussion

This study demonstrates a greater success rate of mifepristone and gemeprost in early legal abortion, compared to the use of gemeprost alone. These results contrast with a smaller study of 49 women, where 1 mg of gemeprost every 3 h to a total of five pessaries was as effective as 150 mg of mifepristone daily for 4 days and 1 mg gemeprost on the third treatment day (Cameron & Baird 1988). The lower analgesic requirement in women treated with mifepristone and gemeprost compared to those treated with gemeprost alone confirms previous results (Cameron & Baird 1988). Analgesic requirements appear to be directly related to the total dose of prostaglandin, whether women are pretreated with mifepristone (Rodger et al. 1989) or given gemeprost alone: 53% of women receiving up to 5 mg gemeprost required opiates analgesics (Cameron & Baird 1988) compared with 36% of the women in the present study who received up to 3 mg gemeprost. A 0.5 mg gemeprost pessary is as effective as 1 mg gemeprost in combination with mifepristone but results in significantly less abdominal pain (Rodger et al. 1989).

In the present study there was no significant difference in the efficacy of 200, 400 or 600 mg mifepristone in combination with 1 mg gemeprost; these data are in agreement with a preliminary report on 1188 women in the multicentre trial, stating the three treatment regimens to be equally effective (Maurice 1991). In a previous study we were unable to demonstrate any significant differences in efficacy between 600, 500 or 400 mg mifepristone (Rodger & Baird 1987) and a WHO supported trial showed that repeated small doses of mifepristone (5 × 25 mg) were as effective as a single 600 mg dose (WHO 1991). Although the data sheet for mifepristone recommends a single 600 mg dose followed 48 h later by 1 mg gemeprost, the present study suggesting that 200 mg dose is effective points to the need for further research to determine the lowest effective dose of mifepristone and prostaglandin.

Haemoglobin levels, hCG levels and duration of bleeding have all been assessed in relation to the first day of treatment (day 1), although most of the abortions occurred on day 1 in the gemeprost alone group, and on day 3 in the mifepristone and gemeprost group. Median hCG concentrations were lower 7 days after the start of treatment in the group treated with gemeprost alone, compared with the group of women treated with mifepristone and gemeprost, despite the fact that the former group includes a greater proportion of women with an ongoing pregnancy. In women treated with gemeprost alone, a significant decrease in hCG concentration is seen 24 h after treatment, whereas in women treated with mifepristone and gemeprost, hCG does not decline until prostaglandin is given (day 3) and abortion occurs (WHO 1989). The difference in

Table 2. Initial outcome of treatment with gemeprost alone or mifepristone and gemeprost

<table>
<thead>
<tr>
<th>Outcome of treatment</th>
<th>Gemeprost alone (n=151)</th>
<th>Mifepristone and gemeprost (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of women (95% CI)</td>
<td>% of women (95% CI)</td>
</tr>
<tr>
<td>Complete abortion</td>
<td>87.4 (84.7–90.1)</td>
<td>98.0 (96.9–99.1)</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>6.0 (4.0–7.9)</td>
<td>0.7 (0.0–3.9)</td>
</tr>
<tr>
<td>Incomplete abortion</td>
<td>6.6 (4.6–8.6)</td>
<td>1.3 (0.6–5.0)</td>
</tr>
</tbody>
</table>

*The two women in the mifepristone and gemeprost group who required a hysterectomy curettage are included as incomplete abortions. Data are expressed as percentage of women (95% CI).

Table 3. Analgesic requirements in women treated with gemeprost alone or with mifepristone and gemeprost

<table>
<thead>
<tr>
<th>Analgesia</th>
<th>Gemeprost alone (n=151)</th>
<th>Mifepristone and gemeprost (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>24%</td>
<td>45%</td>
</tr>
<tr>
<td>Paracetamol only</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>Codeine ± paracetamol</td>
<td>33%</td>
<td>18%</td>
</tr>
<tr>
<td>Diamorphine ± codeine ± paracetamol</td>
<td>35%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Significance of difference between the two groups P=0.0001.
Table 4. Point prevalence of pregnancy/prostaglandin related symptoms at 0, 6 and 12 h after the first prostaglandin pessary in 117 women treated with gemeprost alone.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Time in relation to first pessary (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (32%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Prurit pain</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>42 (36%)</td>
</tr>
<tr>
<td>Weakness</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Data are expressed as numbers of women and percentages in brackets.

Significance of difference between symptoms at time 0: * P <0.02, ** P <0.001, *** P <0.002, **** P <0.0002.

hCG concentrations between these two groups reflects the later occurrence of abortion in women treated with mifeprisone and gemeprost. The change in hCG concentration 7 days after prostaglandin administration in each group might have been a more valid comparison. Otherwise, the effects of both treatments in terms of duration of bleeding and interval to next menses (both measured from the start of treatment rather than the day of abortion) were remarkably similar.

Previous protocols using gemeprost in early legal abortion in this centre have employed a regimen, with a total dose of up to 5 mg prostaglandin (Smith & Baird 1980; Cameron & Baird 1988). This regimen, of 1 mg every 6 h to a total of 3 mg gemeprost was chosen in an attempt to reduce prostaglandin side effects. Although a direct comparison with surgical abortion was not made here, the relatively low complete abortion rate of 87% associated with prostaglandin-induced abortion supports the conclusion from smaller studies that vacuum aspiration under general anaesthesia is more effective than medical termination of pregnancy using gemeprost alone (Smith & Baird 1980).

The increase in the prevalence of prostaglandin related side effects following the first pessary (nausea, abdominal pain, hot flushes and diarrhoea) is expected, the significant decrease in breast tenderness presumably indicates a fall in hormonal levels as separation of the conceptus and abortion occurs.

The lower mean weight of women who aborted after treatment suggests that the dose/kg and/or the plasma profile of gemeprost is important, perhaps resulting in a greater "prostaglandin impact" in women who aborted successfully after treatment with gemeprost (Caspo 1972). Despite a greater height and a lower weight in women who aborted after gemeprost alone, there was no difference in body mass index (weight/height², Quetelet's index). This contrasts with published data on the predictors of failed attempted abortion with the antiprogesterone mifeprisone, with or without prostaglandin (Grimes et al. 1990). There was no significant difference in mean gestation in women who aborted, compared to those who did not. The earlier interval to bleeding and the increased analgesic requirement in women who aborted after prostaglandin therapy suggests a greater sensitivity to prostaglandin.

Table 5. Characteristics of women who aborted completely after gemeprost alone (successful), compared to those who did not (unsuccessful).

Data are expressed as means (95% CI), except for parity (percentage) and medians and range for: initial hCG, hCG on day 2 and day 8 and change in haemoglobin concentrations. The probabilities of a significant difference is shown in the last column as determined by analysis of variance, except for parity (χ² test), and hCG, change in serum hCG and change in haemoglobin concentrations (Mann-Whitney U test).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful (n=132)</th>
<th>Unsuccessful (n=19)</th>
<th>P</th>
<th>Significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25-6 (24-2 to 27-1)</td>
<td>24-3 (22-3 to 26-42)</td>
<td>ns</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163-9 (162-8 to 164-9)</td>
<td>157-87 (146-3 to 169-5)</td>
<td>&lt;0.05</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61-3 (59-3 to 63-3)</td>
<td>60-1 (57-5 to 67-7)</td>
<td>&lt;0.05</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Gestation (days)</td>
<td>47-7 (46-8 to 48-6)</td>
<td>45-0 (42-7 to 47-4)</td>
<td>ns</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Parity</td>
<td>45%</td>
<td>32%</td>
<td>ns</td>
<td>χ²</td>
</tr>
<tr>
<td>Serum hCG</td>
<td>38 960</td>
<td>31 150</td>
<td>ns</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>% of initial value</td>
<td>(339-214 000)</td>
<td>(706-136 500)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On day 2</td>
<td>34-1 (7-8 to 1267)</td>
<td>58-9 (28-5 to 103-2)</td>
<td>&lt;0.0001</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>On day 8</td>
<td>1-7 (0-5 to 113-6)</td>
<td>90-7 (9-9 to 277-0)</td>
<td>&lt;0.0001</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Change in hCG</td>
<td>-0-3 (-1-6 to 1-0)</td>
<td>-0-5 (-1-4 to 0-2)</td>
<td>ns</td>
<td>Mann-Whitney</td>
</tr>
</tbody>
</table>

Data are expressed as means (95% CI) except for parity (%) and medians (range for serum human chorionic gonadotrophin (hCG) levels and change in haemoglobin (Hb) concentrations.
glandin in these women. The greater decrease in serum hCG in women who do abort is apparent as early as 24 h after treatment (P<0.0001).

These data show clear advantages of mifepristone and prostaglandin in early legal abortion compared to prostaglandin treatment alone. Most women undergoing terminations of pregnancy using gemeprost alone who required all three pessaries had an overnight stay in hospital, which is not only inconvenient for many women, but has obvious cost implications. This was not a feature of termination of pregnancy using mifepristone and gemeprost. The lower analgesic requirement in women receiving the combination of mifepristone and gemeprost implies lower perceived pain, and therefore greater patient acceptability, than the use of gemeprost alone. Mifepristone and gemeprost is likely to be the method of choice for early medical abortion, but where gemeprost is unavailable or contraindicated, 1 mg of gemeprost every 6 h may provide a useful alternative.

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The Efficacy and Tolerance of Mifepristone and Prostaglandin in Termination of Pregnancy of Less Than 63 Days Gestation; UK Multicentre Study—Final Results

Investigators and Centres:
DR Urquhart, AA Templeton, University Department of Obstetrics & Gynaecology, Aberdeen; F Shinewi, M Chapman, Guy’s Hospital, London; K Hawkins, J McGarry, Barnstaple General Hospital; M Rodger, DT Baird, Centre for Reproductive Biology, Edinburgh; S Bjornsson, M Macnaughton, CB Lunan, The Royal Infirmary, Glasgow; P Macrow, M Elstein, S Killick, University Hospital of South Manchester, NCW Hill, AC Turnbull, IZ MacKenzie, John Radcliffe Hospital, Oxford; M Cohn, P Stewart, Northern General Hospital, Sheffield; F Bryce, RJ Liford, N Johnson, St James’s University Hospital, Leeds; TC LJ, ID Cooke, Jessop Hospital for Women, Sheffield; F Olajide, T Chard, St Bartholomew’s Hospital, London; B Lim, DAR Leas, Raigmore Hospital, Inverness; V Subramanayan, JG Grudzinskas, The Royal London Hospital, Whitechapel, London; A Davey, Hoechst Marion Roussel, Denham, Middx

This paper summarizes the final results of an open multicenter study in 13 hospital gynaecological units in Scotland and England. In the study, 1018 pregnant women with up to 9 weeks amenorrhoea received 600 mg oral mifepristone followed 48 h later by vaginal gemeprost 1 mg, for the induction of first trimester abortion.

Outcome was measured by assessment of the frequency of complete abortion or the need for subsequent surgical evacuation. Tolerance was assessed in terms of pain, requirement for analgesia, bleeding, and other adverse effects.

There was complete abortion in 94.8% (95% CI 93.4–96.2); surgical evacuation was performed in 5.2% of patients. There was no relationship between outcome and age of gestation on the day mifepristone was given. Seven women were given a transfusion. Narcotic analgesia was administered after gemeprost to 38.1% of nullipara and 10.7% of multipara. Mifepristone and prostaglandin is an effective and acceptable alternative to surgical termination of pregnancy in the early first trimester.

KEY WORDS: mifepristone, gemeprost, termination of early pregnancy, efficacy, tolerance.

Introduction

Mifepristone (RU38,486; 17β-hydroxy-11β-[4-dimethylaminophenyl]-1-7α[prop-1-ynyl]-estr-4-9-dien-3-one; Roussel Uclaf) is a synthetic nonsteroid which acts by reversible binding to steroid receptors. It has a high affinity for the progesterone receptor. The ability of mifepristone to block the action of progesterone on the pregnant uterus has led to the development of its use as an abortifacient.

The success of mifepristone alone for induction of abortion has been extremely variable and has never exceeded 88%. However, the combination of mifepristone with a small dose of prostaglandin has proved much more effective at gestations of up to 8 weeks.

This is the final report of a large multicentre study designed to assess the efficacy and tolerance of mifepristone in sequential use with a prostaglandin (gemeprost) in the termination of first trimester pregnancy. An earlier report on the first 588 women participating in the study has already been published.

Our aims in reporting this study are to update the findings of the earlier publication.
Materials and Methods
The study was an open, multicentre hospital investigation to assess the efficacy and tolerance of the sequential administration of mifepristone and vaginal prostaglandin in the termination of pregnancy of up to 9 weeks amenorrhoea.

Consenting women over the age of 18 years with pregnancies of 63 days gestation or less (as assessed by date of last menstrual period and ultrasound scan) were eligible for inclusion. Women who had taken any medication in the 12 h prior to mifepristone administration or were taking medication which may affect the outcome of pregnancy or study treatment were excluded from the study, as were women who had been treated with glucocorticoid drugs within the previous year, had any previous obstetrical complications, a history of serious disease, hyper-sensitivity to previous medications, or who had an abnormal hematological or biochemical profile which may have made assessment of response to study treatment difficult to evaluate.

Women received a single oral 600-mg dose of mifepristone, followed 48 h later by a 1-mg vaginal pessary of gemeprost. Women were scheduled to be reviewed every 7 days over the course of the next 4 weeks to determine efficacy and tolerance. Assessments were performed to establish efficacy and tolerance of the treatment and included full biochemical and hematological screening, quantitative β-HCG, and ultrasound scans, as well as observational recording of signs and symptoms, and requirement for analgesia. Outcome was considered to be “successful” if surgical intervention was not required. Requirement for surgical intervention was based on the judgment of the investigator who considered the patient's physical signs and symptoms, well-being, results of ultrasound scanning, and any appropriate social factors. Full details of the study design and methodology have been previously described.9

Results
Overview of Study Population
Over the course of the study, 1018 women were recruited from a total of 13 centres in the UK. Thirty-three women withdrew from the study before receiving mifepristone, 25 women decided not to take part in the study, and eight were withdrawn for the following reasons: two were not pregnant, three had pregnancies of greater than 63 days gestation, one had a spontaneous abortion, one had a previous allergic reaction to metaclopromide, and one had a haemoglobin of <10 g/dl. A further two patients, who received mifepristone and prostaglandin, were not included in the analysis, one was subsequently diagnosed as having an ectopic pregnancy and the other a pseudo-pregnancy. Eight women received mifepristone but withdrew before administration of prostaglandin, for the following reasons: five women vomited shortly after taking mifepristone and were, therefore, referred for a surgical termination; one woman requested a surgical termination; and two women decided to continue their pregnancies, both of whom continued successfully to term with uneventful outcomes.10

Patient Characteristics
The median age was 24, with a range of 16-49 years. Although the intention was to restrict recruitment to women aged ≥18 years, seven women aged 16 or 17 were treated and have been included in the analysis.

Of the 1018 women recruited, 384 (37.7%) had one or more previous vaginal deliveries. Forty-six women had had a previous caesarean section. Two hundred seventy-six (27.1%) had had one or more previous abortions and of these, 197 (71.4%) had been by vacuum aspiration and/or prostaglandin; unrecorded in 28.6%.

The gestational age at the time of termination is given in Table 1. Thirty-one pregnancies were of ges-

<table>
<thead>
<tr>
<th>Gestational Age (days from LMP)</th>
<th>Total Number of Women (% of total)</th>
<th>Women Evaluable for Efficacy (% of total)</th>
<th>Number of Surgical Intervention (proportion of number in group %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;36</td>
<td>16 (1.6)</td>
<td>13 (1.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>36–42</td>
<td>80 (7.9)</td>
<td>69 (7.2)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>43–49</td>
<td>275 (27.3)</td>
<td>255 (26.6)</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td>50–56</td>
<td>408 (40.1)</td>
<td>393 (41.1)</td>
<td>21 (5.3)</td>
</tr>
<tr>
<td>&gt;57</td>
<td>235 (23.1)</td>
<td>227 (23.7)</td>
<td>15 (6.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1018</td>
<td>957</td>
<td>50 (p = 0.25)</td>
</tr>
</tbody>
</table>

*No significant relationship between age of gestation and surgery.
tational age 64–70 days, although outside the inclusion criteria, data from these patients were included in the analysis.

Efficacy

Of the 975 women who received mifepristone and were eligible for prostaglandin, 18 were unevaluable for calculation of the abortion success rate (five women received two prostaglandin pessaries, 13 were not examined at follow-up). Data from 957 women were, therefore, evaluable for efficacy. Of these, 907 (94.8%, 95% CL 93.4–96.2%) were assessed by the investigator to have aborted successfully with no serious complications. Fifty patients (5.2%) underwent a subsequent surgical procedure. Three (0.3%) women required suction termination of ongoing pregnancy at follow-up. Six women underwent surgical evacuation of the uterus within a few hours after the administration of gemeprost, four because of hemorrhage and two (one a twin pregnancy) for social reasons. The main reason for intervention in the remainder of cases where this was performed were signs and symptoms (continued bleeding, continued pain, symptoms of infection, bulky uterus, open cervix, etc.) or ultrasound images suggesting incomplete abortion. The timing of intervention is shown in Table 2. The decision to refer for surgical evacuation of the uterus was not reliant on any single measurement but depended largely on an assessment of the clinical signs and symptoms, or adverse events in relation to time after administration of the prostaglandin.

There was no significant relationship between pregnancy gestation and the rate of intervention (p = 0.25) [Table 1]. Similarly, there was no relationship between parity and the requirement for surgery.

In the clinicians’ opinion, 10 women (1%) had aborted completely within 48 h after administration of mifepristone. Nine of these women did not receive prostaglandin. A further two women in whom abortion had partially occurred were not given prostaglandin. In these two women, abortion was complete by follow-up, 9 days after administration of mifepristone.

In a total of 783 patients (81.5%), abortion was confirmed to be complete by the time of the first follow-up (9 days after administration of mifepristone).

Eight hundred thirty-three women (94.9%) had an ultrasound scan at assessment 4 (7 days post prostaglandin); retained products of conception were diagnosed in 59 (7%) women, of whom 14 were referred for evacuation of the uterus, the remainder were managed conservatively. In total, ultrasound scans were diagnostically helpful in only 19 of the 38 cases requiring surgical evacuation of the uterus either at assessment 4 or at later follow-up.

Measurement of hCG levels did not prove to be a useful indicator of efficacy. In a substantial number of women, although levels decreased, values remained above the level usually indicative of pregnancy throughout the study period.

A total of 261 women (26.7%) stayed in hospital longer than 4 h after prostaglandin administration, although most had been discharged within 8 h. Seventeen remained for 9–48 h. Reasons most commonly given for extended stay were that products of conception had not been passed, women were drowsy after narcotic analgesia, or were experiencing vaginal bleeding or abdominal pain.

Tolerance

BLEEDING. Of the 964 women who received both mifepristone and prostaglandin, seven women attended an unscheduled assessment 24 h following mifepristone administration due to heavy bleeding; five of these women were given the prostaglandin pessary at this time (i.e., 1 day early) and all cases aborted completely.

Five hundred forty-six women (56.5%) experienced some bleeding prior to administration of gemeprost. The majority of women who were not already bleeding, began to bleed by 2 h following prostaglandin administration. Bleeding tended to increase from spotting/light before prostaglandin to light/moderate at 4 h post prostaglandin. Ninety patients (9.4% of those recorded) complained of severe or excessive bleeding.

Seven women received a blood transfusion for heavy vaginal bleeding, four shortly after administration of the prostaglandin pessary and three at 2, 11, and 15 days following prostaglandin treatment, respectively.

The women kept a daily record of the incidence and severity of bleeding for 14 days after receiving prostaglandin. By 5 days after administration of gemeprost, 660 women (75.6%) had ceased to bleed or

<table>
<thead>
<tr>
<th>Days Following Medical Termination</th>
<th>Number of Women</th>
<th>% of Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>1–6</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>7–14</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>15–28</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>&gt;28</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>51*</td>
<td>100</td>
</tr>
</tbody>
</table>

*50 Evaluable, 1 not evaluable.
had light bleeding or spotting only; this figure had increased to 694 (91.6% of those for whom the data were recorded) by day 9. At day 9, 0.7% of women complained of severe or excessive bleeding.

Measurement of changes of hemoglobin levels in 955 women showed that in 708 (74%) the fall was less than 1 g/dl, while in 2.1% of women there was a decrease of > 3 g/dl.

PAIN. The severity of abdominal pain was assessed subjectively by women at various intervals up to 14 days following medical termination. In the 48 h following mifepristone administration, 522 (54.2%) women experienced some pain. In the majority of women (95.4%), pain was mild or moderate; 24 (4.6%) experienced severe pain. Following prostaglandin administration, the incidence and severity of pain reached a maximum at 2 h when 537 women [56% of those for whom data were recorded] complained of moderate or severe pain. By 4 h, this had fallen to 299 (31.2%), and at 2 days after administration of prostaglandin, this had fallen further to 180 women (20.7%). Nine days after administration of prostaglandin, 1.5% of women reported moderate pain, there were no reports of severe pain.

Narcotic analgesia was administered to 275 women (28.5%) in the 4 h after administration of gemeprost. Two hundred eighty-six women (29.6%) received non-narcotic analgesia and 405 (41.9%) none. Narcotic analgesia was administered to 38.1% of nulliparous women and 13.3% of parous women. Analgesia requirement appeared to be related to prior menstrual symptoms. 55.9% of women with a history of severe dysmenorrhea received narcotic analgesia compared with 23.2% of women with no such history.

Important symptoms other than pain and bleeding included vomiting, diarrhea and headache (Table 3). Vomiting and diarrhea were associated with administration of gemeprost; in the 4 h following administration, 23.3% of women vomited and 11.2% had diarrhea.

Discussion

The efficacy and tolerance of the sequential administration of mifepristone and prostaglandin for medical termination of early pregnancy has been established through clinical trials and routine use. Since the interim findings of this study were published, 9 results of additional research have been presented. This publication makes available to medical practitioners additional information on the clinical use of mifepristone 600 mg for medical termination of pregnancy.

The results presented here, although similar, differ in some respects from those of the interim report. 9 A small increase in the efficacy rate has been achieved, complete abortion occurring in 94.8% of women as opposed to the 94.0%. This increase may reflect increasing clinical confidence and experience. In the interim analysis, 23 women out of 588 (5.9%) had surgery, while in the latter part, 14 out of 387 (3.6%) were withdrawn for surgery. This gives an overall withdrawal rate of 5.2% (51/975) but suggests that over the course of the study, as clinical experience increased, this declined. Where intervention did occur, it was generally delayed until later, doctors being more willing to manage patients conservatively.

The earlier analysis suggested that efficacy may be related to gestational age, however, although a trend appears to exist, this is not statistically significant. The results presented here confirm earlier findings on tolerance. In the final analysis, the requirement for transfusion was 0.7% as opposed to 0.9% in the interim report. In all other respects, tolerance was similar in the two analyses.

The majority of the adverse events are related to the administration of the prostaglandin (gemeprost). Two publications 11,12 suggest that tolerance is improved by the use of the orally active prostaglandin, misoprostol, in sequential administration with mifepristone. However, other data 13 show that the efficacy of 200 mg mifepristone given in association with 600 µg oral misoprostol for termination of pregnancies up to 56 days gestation is less than that associated with the regimen adopted in this study. Usage of misoprostol via the vaginal route has now been suggested to increase the efficacy of the regimen. 14

Since the completion of this study, further work has been presented 15-17 comparing medical and surgical methods of termination, which has shown no differences in terms of efficacy, short-term medical complications, and early psychological morbidity between the two methods. At follow-up, however, antibiotics were prescribed for suspected vaginal infection significantly more frequently in the groups undergoing vacuum aspiration. 15,16 Patient acceptability is strongly linked to initial patient preference and highlights the importance to women of choice and appropriate counseling.
Conclusion
The sequential administration of mifepristone and prostaglandin is an effective, well-tolerated, acceptable, and cost-effective method for the termination of first trimester pregnancy. It is not a replacement for surgical termination, but an alternative, which is requested by a proportion of women and allows them a choice in their treatment.

References
4. Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with an antiprogestogen RU486 alone or in combination with prostaglandin analogue (gemeprost). Contraception 1986;34:559-68.
Validation of the Alkaline Haematin Technique.

Menstrual Blood Loss

The reliability of the alkaline haematin technique is illustrated below

<table>
<thead>
<tr>
<th>ADDED (mls)</th>
<th>RECOVERED (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5.3 ± 0.4</td>
</tr>
<tr>
<td>10</td>
<td>10.0 ± 0.3</td>
</tr>
<tr>
<td>20</td>
<td>20.8 ± 0.6</td>
</tr>
<tr>
<td>40</td>
<td>40.6 ± 0.6</td>
</tr>
<tr>
<td>60</td>
<td>61.8 ± 1.5</td>
</tr>
</tbody>
</table>

For each volume of blood added, the amount recovered represents the mean ± standard error of six experiments.

(From: Cameron, I.T., MD Thesis; University of Edinburgh, 1987)