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Mid-trimester induced abortion: a review

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Mid-trimester abortion constitutes 10–15% of all induced abortion. The aim of this article is to provide a review of the current literature of mid-trimester methods of abortion with respect to efficacy, side effects and acceptability. There have been continuing efforts to improve the abortion technology in terms of effectiveness, technical ease of performance, acceptability and reduction of side effects and complications. During the last decade, medical methods for mid-trimester induced abortion have shown a considerable development and have become safe and more accessible. The combination of mifepristone and misoprostol is now an established and highly effective method for termination of pregnancy (TOP). Advantages and disadvantages of medical versus surgical methods are discussed. Randomized studies are lacking, and more studies on pain treatment and the safety of any method used in patients with a previous uterine scar are debated, and data are scarce. Pain management in abortion requires special attention. This review highlights the need for randomized studies to set guidelines for mid-trimester abortion methods in terms of safety and acceptability as well as for better analgesic regimens.

Key words: dilatation and evacuation/mid-trimester induced abortion/mifepristone/misoprostol/vacuum aspiration

Introduction

Abortion is defined as 'termination of pregnancy (TOP) by any means before the fetus is viable'. Viability is now considered to be reached at 23–24 weeks of gestation. Second trimester, or mid-trimester, is a period ranging from 13 to 28 weeks of gestation, which again is subdivided into an early period between 13 and 20 weeks and a late period between 20 and 28 weeks. In this review, we have limited late abortions up to 24 weeks gestation.

TOP by induced abortion is practised worldwide. Induced abortion, either elective or therapeutic termination of a viable pregnancy, is one of the most ancient procedures. Of the 210 million pregnancies that occur each year, >46 million (22%) end in induced abortions (Alan Guttmacher Institute, 1999). A majority (90%) of the terminations take place in the first trimester. Worldwide mid-trimester abortion constitutes 10–15% of all induced abortions but is responsible for two-thirds of all major complications (WHO, 1997). Although the majority of abortions are performed in the first trimester, there is still a gradual increase in second-trimester abortion because of the wide scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities such as cardiovascular and skeletal malformation.

Over the last 20 years, there have been continuing efforts to improve the abortion technology in terms of effectiveness, decreasing rates of complications, technical ease of performance and acceptability. During this time, >20 countries have partially or fully liberalized their abortion laws (Berer, 2004). Today, in almost all countries, the law permits abortion to save a pregnant woman's life. However, the requirement of legalization is no guarantee for a safe abortion. In many countries where abortion is illegal, as in Latin America, private physicians often perform safe abortions for relatively high medical fees, and the law is rarely enforced (Fathalla, 1997). The larger population, which cannot afford such fees, succumb to the cheaper ways of abortion practices that eventually risk their lives. This may be because of lack of safe services provided in the public sector and lack of access to referral units that exist. Today, in most cases, safe and efficient abortion services can be offered or improved by minor changes in existing healthcare facilities.

Aim of the study

The aim of this study is to provide a review of the current literature on mid-trimester methods of abortion with respect to efficacy, side effects and acceptability and also to provide evidence-based recommendations for safe regimen(s) for mid-trimester pregnancy terminations.

Materials and methods

Search criteria

Electronic literature search (English) of MEDLINE database using following keywords: Mid-trimester induced abortion, second-trimester pregnancy termination, induced abortion, mifepristone,

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misoprostol, gemeprost, medical abortion in prior Caesarean section (CS) and pain management.

Types of studies

All randomized controlled trials, large case series with data on mid-trimester TOP.

Types of outcome measures

Primary outcomes:

(i) Rate of complete abortion.
(ii) Failure to achieve complete abortion with intended method.
(iii) Induction-to-abortion interval.

Secondary outcomes:

(i) Safety of the method/regimen used.
(ii) Acceptability of the method used.
(iii) Excessive blood loss either measured or estimated by a clinically relevant drop in haemoglobin.
(iv) Pain resulting from the procedure, reported by the women or measured by use of analgesics.
(v) Post-abortion curettage required in women with medical abortion method.
(vi) Side effects such as pyrexia, nausea, vomiting and diarrhoea.
(vii) Uterine rupture.
(viii) Infectious morbidity.
(ix) Mortality.
(x) Any other grave complication.

Background

Abortion dates back to the period of Socrates, Plato, Aristotle and Hippocrates (Anonymous, 1995). Different surgical and medical methods of abortion have been used since the early age. Surgical abortion is one of the oldest and most commonly practised techniques in many parts of the world. A matter of great concern was that there were no safe drugs for inducing an abortion. Since ancient time, women have used various herbs, salts, douches and purgatives, all with questionable success to achieve pregnancy termination (Riddle *et al.*, 1993). In recent years, effective medical abortion methods with low morbidity have been emerging and become better accessible (Figure 1).

In the early 1970s, the most commonly used methods were vacuum aspiration (VA), dilatation and curettage, sharp curettage, hysterotomy (sectio parva), intra-amniotic injection of hypertonic saline or hyperosmolar urea, intra- or extra-amniotic administration of ethacryidine lactate (Rivanol), parenteral, intra-amniotic or extra-amniotic administration of prostaglandin (PG) analogues and i.v. or i.m. administration of oxytocin (WHO, 1997). Rivanol is a dye with antiseptic properties and seems to be less toxic than hypertonic saline. As with hypertonic saline, Rivanol stimulates endogenous PG and thromboxane production, probably because of chemical trauma to the fetal membranes and the decidua, promoting cervical priming and initiating labour. The instillation to delivery interval ranged from 25 to 40 h (Ingemarsson, 1979; Bhathena *et al.*, 1990; Blumenthal *et al.*, 1999) which could be reduced to 15–20 h with concomitant use of oxytocin (Yapar *et al.*, 1996). Among the drawbacks of all these medical methods are the need for puncture of the intra-amniotic space or the introduction of a Foley catheter into the extra-amniotic space, a relatively long induction-to-abortion interval and the need for curettage after the expulsion of the fetus (Bygdeman, 1983). The i.v. infusion of oxytocin was inconvenient to use because of the serious side effects of water intoxication. The risk of disseminated intravascular coagulation with hypertonic saline is 0.8% (Edelman *et al.*, 1976). This is because of rapid intravascular absorption of hypertonic saline from the amniotic cavity or inadvertent i.m. or i.p. injection of saline resulting in hypernatremia and necrosis of the affected tissue. Thus, many of these methods were very cumbersome in respect of their side effects and medical expertise required.

With the introduction of PGs and later PG analogues, the efficacy of medical abortion could be improved, and the risk for complications and side effects was reduced. The method of medically induced abortion could be further improved as mifepristone became available in the 1980s (Bygdeman and Swahn, 1985; Urquhart and Templeton, 1987; Swahn and Bygdeman, 1988; Silvestre *et al.*, 1990; Gottlieb and Bygdeman, 1991). With mifepristone, the induction-to-abortion interval was shortened, and the dose of PG analogues required was reduced. Today, medical abortion is the method of choice in many centres [Royal College of Obstetricians and Gynaecologists (RCOG), 1997].

PGs and PG analogues

PGs play an important role in the regulation of uterine contractility during pregnancy (Mitchell, 1987). The receptors are present throughout the pregnancy; hence, PGs and their analogues are effective for TOP. Naturally occurring PGs, mainly prostaglandin

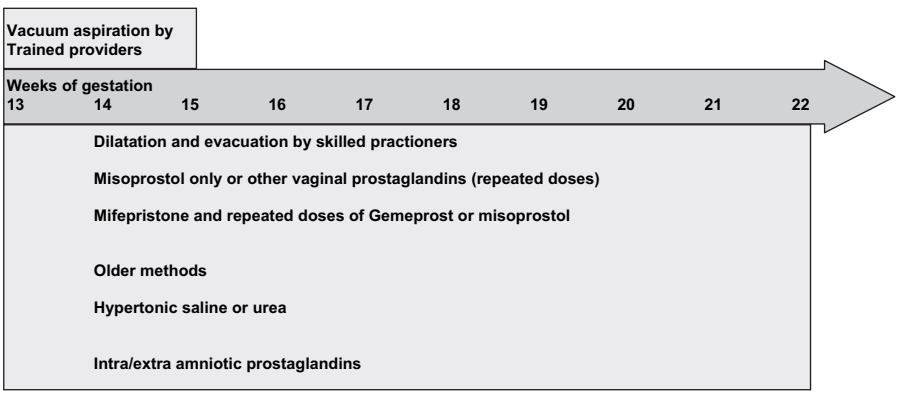

Figure 1. Second trimester methods of abortion.

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E_1 (PGE_1), PGE_2 and $PGF_{2\alpha}$, are potent stimulants of uterine contractility at any stage of pregnancy and also cause cervical ripening and dilatation. However, because of the rapid metabolism and high incidence of gastrointestinal side effects, they had a limited role in induced abortion and were soon replaced by PG analogues that are more suitable for clinical application (Gillet *et al.*, 1972; Wiqvist *et al.*, 1972; Lauersen *et al.*, 1975). The PG analogues, besides being suitable for administration by non-invasive routes, have a prolonged action as they are relatively resistant to the initial rapid inactivation in the circulation (because of the introduction of a methyl group at C15 or C16). Both PGE and PGF analogues are widely used for TOP, although PGE analogues are preferred because of their selective specificity for the myometrium and fewer gastrointestinal side effects (World Health Organization Task Force on Prostaglandins, 1988). The most extensively studied PG analogues are carboprost, sulprostone, gemeprost and misoprostol.

Carboprost, a 15(S)-15-methyl $PGF_{2\alpha}$, was the first analogue to be tested clinically on a large scale for the termination of second-trimester pregnancy. It is used either intra-amniotically (viable second-trimester pregnancy) or administered by i.m. injection. It is of limited value as a primary method for abortion because of its association with high rates of gastrointestinal side effects but may be used when other methods have failed (Lauersen and Wilson, 1976; World Health Organization Task Force on Prostaglandins, 1977a). Both carboprost and another PG analogue meteneprost have been tried in the form of vaginal gel in large multicentre trials, and the effects have been similar to the i.m. route (Bygdeman *et al.*, 1975; World Health Organization Task Force on Prostaglandins, 1977b; Green *et al.*, 1988).

Sulprostone, a 16phenoxy-w-17, 18, 19, 20-tetranor PGE_2 methyl sulphonylamide, was used in the 1980s for the termination of second-trimester pregnancy (World Health Organization Task Force on Prostaglandins, 1982, 1988). It was withdrawn from the market because of its association with severe cardiovascular complications, including myocardial infarction attributed to coronary spasm (Ulman *et al.*, 1992; Peyron *et al.*, 1993). No such similar complications have been reported with other PGs.

Gemeprost is a PGE_1 analogue (16, 16-dimethyl-trans-d2-PGE_1 methyl ester) and is used as a vaginal pessary. It has been extensively used as a non-surgical method to dilate the cervix before VA in late-first and early-second-trimester abortion (Smith and Baird, 1980; Welch and Elder, 1982). As a method for TOP in the second trimester, it has been well established that gemeprost is more efficacious when compared with intra-amniotic $PGF_{2\alpha}$ or extra-amniotic PGE_2 and dinoprostone intracervically (Cameron and Baird, 1984; Andersen *et al.*, 1989; Kjolhede *et al.*, 1994).

Misoprostol is a synthetic PGE_1 analogue (15-deoxy-16-hydroxy-16-methyl PGE_1), initially developed for the prevention and treatment of peptic ulcer and later used off-label as an abortifacient. It has several advantages over other PGs; it is cheap, stable at room temperature and can be stored for a long time. Misoprostol has a limited effect on the bronchi or blood vessels. The oral tablets are effective in different routes of administration. Misoprostol in the required doses has only few (and dose-dependent) side effects, and it is readily available in many countries (http://www.gynuity.org/documents/miso_approval_2004_map_ revised_12.05.pdf).

Pharmacokinetics of misoprostol

Misoprostol is rapidly absorbed after oral administration, primarily metabolized in the liver and converted to its pharmacologically active metabolite, misoprostol-free acid. Less than 1% of this metabolite is excreted in urine. The plasma concentration of misoprostol acid after oral administration peaks at ~30 min and declines rapidly thereafter with a terminal half-life of 20–40 min, whereas after vaginal administration, the levels increase gradually and reach maximum levels after 70–80 min but remain detectable for a significantly longer time. There is a high variability of plasma levels of misoprostol acid between and within studies (Foote *et al.*, 1995; Zieman *et al.*, 1997). Pharmacokinetic studies show that the systemic bioavailability of vaginally administered misoprostol is three times higher than that of orally administered misoprostol. With vaginal administration, peak plasma levels occurred later and were lower, but elevated plasma levels were sustained for at least up to 4 h (Zieman *et al.*, 1997; Danielsson *et al.*, 1999; Tang *et al.*, 2002). A study on the pharmacokinetics following the sublingual, vaginal and oral routes of misoprostol administration for medical abortion demonstrated that sublingual misoprostol reached peak concentration in the shortest time and had the highest bioavailability (Tang *et al.*, 2002). It was shown that the time to peak concentration after sublingual administration was similar to the oral route, but plasma concentration achieved was higher and sustained. Sublingual misoprostol had a higher serum peak concentration and bioavailability (measured as the area under the curve for the plasma levels) compared with vaginal administration.

Effects of misoprostol on uterine contractility

The ideal agent for the induction of abortion is one that gives rise to uterine contractions subsequent to effective cervical dilatation. PG analogues induce cervical ripening both by a direct effect on the cervix and by a concomitant stimulation of myometrial activity (Uldbjerg and Ulmsten, 1990; El-Refaey *et al.*, 1994). The effect of misoprostol on uterine contractility following different routes (sublingual, vaginal and oral) of administration has been well documented (Aronsson *et al.*, 2004). The time from the start of the treatment to the onset of effect (increase in uterine tonus) and to maximum tonus elevation was shorter with oral and sublingual compared with vaginal administration. The study also showed that after a single oral administration of misoprostol, regular uterine contractions did not develop. Following sublingual and vaginal administration, on the contrary, increased uterine contractility was observed 2 h after administration. The effect on uterine contractions after sublingual administration seemed to be shorter lasting than that seen following vaginal administration. This effect would probably be more significant for misoprostol-only regimens that require more repeated doses of misoprostol to achieve the clinical outcome. For regimens with mifepristone pretreatment, the doses of misoprostol required are usually less, and therefore, sublingual or even oral misoprostol may be enough. Sublingual misoprostol was considered to be more convenient and less uncomfortable but associated with bad taste and a higher frequency of side effects (Tang *et al.*, 2004). The most commonly encountered side effects were fever, shivering, vomiting and diarrhoea. Another advantage with the oral/sublingual route is

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that the absorption of the drug is not affected if the woman starts to bleed. This is especially true when the repeated administration of misoprostol is required.

Antiprogesterone

Progesterone is a key hormone in maintaining the pregnancy by keeping the uterus in a quiescent state. Progesterone prevents softening and dilatation of the cervix, it reduces PG output from the decidua, and it suppresses uterine contractions by inducing hyperpolarization of the cell membrane, which makes the myocytes less sensitive to electrical stimulation. Furthermore, progesterone induces the inhibition of gap junction formation resulting in the counteraction of co-ordinated uterine contractions. Progesterone antagonists are synthetic steroids that bind to the progesterone receptors and prevent endogenous progesterone from exerting its action (Van Look and Bygdeman, 1989). Mifepristone is the only anti-progestin approved for the induction of abortion. It is a 19-norsteriod substituted at the 11β position by a *p*-dimethylamino phenyl group, which binds with high affinity to the progesterone receptor, thus inhibiting the effect of the hormone. Its binding affinity for the progesterone receptor is 2.5–5 times that of progesterone (Lähteenmäki *et al.*, 1987). Blockage of the progesterone receptor results in vascular damage, decidual necrosis and bleeding (Bygdeman and Swahn, 1985; Johansson *et al.*, 1989). Treatment with mifepristone will soften the cervix, increase the sensitivity to PGs and convert the quiet pregnant uterus into an organ of spontaneous activity (Bygdeman and Swahn, 1985; Swahn and Bygdeman, 1988; Norman *et al.*, 1991). The sensitivity of the myometrium is increased by ~5 times with maximal effect on uterine contractility and cervical ripening at 36–48 h following treatment (Bygdeman and Swahn, 1985; Rådestad *et al.*, 1988). The benefits of pretreatment with mifepristone in comparison with placebo and laminaria tent are well evidenced (Table I, Panels a and b). Mifepristone and a PG analogue act in synergy, thus a change in the dose/type of one drug or in the route of administration and interval between the mifepristone and PG analogue will have impact on the required dose of the other and the subsequent efficacy and side effects.

The pharmacokinetics of mifepristone is linear up to doses of 100–200 mg, and above that, it is non-linear (Swahn *et al.*, 1986; Heikinheimo *et al.*, 1987). The approved dose of mifepristone in medical mid-trimester abortion is 600 mg (similar to early medical abortion), but it has been shown that the abortion rate and induction-to-abortion interval were the same even if the dose was reduced to 200 mg (Webster *et al.*, 1996).

Although maximal priming effect on the myometrium is achieved 36–48 h after pretreatment with mifepristone, no difference was seen in induction-to-abortion time with mifepristone administered 24, 36 or 48 h before PG administration that probably depends on the PG dose used (Urquhart and Templeton, 1990a). In another study, a shorter interval resulted in a slightly longer induction-to-abortion interval and higher dose of misoprostol used (Heikinheimo *et al.*, 2004).

Around 0.2–0.4% of women abort with mifepristone only (UK Multicenter Study Group, 1997; Tang *et al.*, 2001). The concept of genetic variation of the progesterone receptor has been postulated in first-trimester abortions among women with a continued pregnancy who did not respond to mifepristone–PG combination. There is a need to look more in depth into failed or prolonged second-trimester abortion (Gao *et al.*, 1998).

Table I. Methods of mid-trimester induced abortion

Author	Trial design	No. of subjects, gestational age (weeks)	Regimen		Abortion rate (%)		Mean/Median PG used	Induction-abortion interval (h) median	Curettage rate for retained products (%)
			Mifepristone dose/time	Prostaglandins dose/route/time	≤24h	≤48 h			
Panel a. Mifepristone versus placebo									
Rodger and Baird (1990)	DB, RCT	100 (12–18)	600 mg mife orally 36 h prior	1 mg geme q3hx5 for both groups	94		3 doses geme	6.8*	92
			Placebo 36 h prior		80		3 doses geme	15.8*	96
Panel b. Mifepristone versus laminaria tents									
Ho *et al.* (1995)	Pros RCT	62 (14–20)	600 mg Mife 36 h prior	1 mg geme q3hx5 for both groups			Few	7.5*	
			Laminaria tent 12 h prior					11*	

q3hx5 is every 3 hourly, maximum five doses.
DB, double blind; geme, gemeprost; mife, mifepristone; PG, prostaglandin; Pros, prospective; RCT, randomized controlled trial.
*Significantly different.

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Medical abortion with mifepristone and a PG analogue

For mid-trimester abortion (13–24 weeks of gestation), medical abortion with mifepristone followed by PG is an appropriate method and has been shown to be safe and effective (RCOG, 2004). It has been well proven that pretreatment with the antiprogesterone mifepristone 36–48 h before PG administration can increase the success rate, shorten the induction-to-abortion interval and reduce the amount of PGs required in second-trimester abortion (Thong and Baird, 1992a; Ho *et al.*, 1995, 1997).

Medical abortion during early pregnancy was first approved in France in 1988 (up to 49 days amenorrhoea) followed by approvals in the UK (1991) and Sweden (1992) (up to 63 days of amenorrhoea in both the countries). A few years later, mifepristone together with a PG analogue was also approved for second-trimester abortion (in Sweden in 1994). Mifepristone has been used in China since 1992. However, it was only in 1999/2000 that both early-first- and -second-trimester medical abortions with mifepristone and PG were approved in several other European countries. Today, mifepristone is available in 29 countries worldwide (http://www.gynuity.org/documents/mife_approval_2005_map.pdf).
Since the introduction of the method, extensive research is ongoing focusing on improving efficacy, defining the optimal dose/type and route of the administration of PG analogue.

Mifepristone and gemeprost

The vaginal gemeprost-only regimens achieved an abortion rate of 88–96.5% with longer induction-to-abortion interval. With pretreatment with mifepristone 36–48 h before gemeprost, the induction-to-abortion could be decreased to nearly half (from 15.7 to 6.6 h), and the abortion rate in 24 h was increased from 72 to 95% (Van Look and Bygdeman, 1989). Furthermore, side effects were reduced, and the dose of mifepristone and gemeprost decreased to one-third and one-half respectively, without the loss of clinical efficacy (Thong and Baird, 1993). In a case series report on 197 consecutive cases treated with mifepristone and gemeprost, a significant correlation between pregnancy length and abortion time was shown (Gemzell-Danielsson and Östlund, 2000). The induction-to-abortion interval was also shorter in parous women. Gemeprost was considered as the standard PG analogue in medical abortion and cervical priming until misoprostol emerged and was made available (Bartley *et al.*, 2001). Although shown to be highly effective, gemeprost has several disadvantages compared with misoprostol (i.e. cost, need for refrigeration limits, its usage in developing countries and it is only available as vaginal pessary), which has replaced gemeprost on all indications.

Mifepristone and misoprostol

Misoprostol has been shown to be equally or more effective compared with gemeprost (Ho *et al.*, 1996; Bartley and Baird, 2002) (Table II, Panel C). In a study of 98 women, it was shown that vaginal misoprostol is more effective than oral misoprostol after pretreatment with mifepristone, but more women preferred the oral route (Ho *et al.*, 1997). The induction-to-abortion interval was shorter, and the amount of misoprostol required was lower after vaginally administered misoprostol (Ho *et al.*, 1997; Ngai *et al.*, 2000) (Table II, Panel b). The incidence of diarrhoea was higher with oral misoprostol. However, women preferred oral to vaginal administration considering it more convenient and giving more privacy (Ho *et al.*, 1997; Ngai *et al.*, 2000). Therefore, to improve acceptability, a regimen using a combination of an initial high dose administered vaginally followed by repeated oral doses of misoprostol was developed, which involved the use of 600 μg of vaginal misoprostol as the first dose followed by 400 μg of oral misoprostol for every 3 h. The abortion rate (97%) and the induction-to-abortion interval (6.5 h) were the same as using similar doses of repeated vaginal misoprostol (El-Refaey and Templeton, 1995) (Table II, Panel b). The results were later confirmed in a larger series of patients using a slightly higher initial dose of 800 μg of vaginal misoprostol (Ashok and Templeton, 1999; Ashok *et al.*, 2004) (Table II, Panel b). It was believed that the use of misoprostol vaginally as the first dose could lead to more effective cervical priming, but there was no advantage in the vaginal administration of subsequent doses (Ashok and Templeton, 1999).

More recently, it was shown that the combination of mifepristone and sublingual misoprostol provides a safe and an effective regimen for medical abortion (Hamoda *et al.*, 2005a; Tang *et al.*, 2005) (Table II, Panel b). In the first randomized study comparing sublingual versus vaginal misoprostol in the second trimester, no pretreatment with mifepristone was given (Tang *et al.*, 2004) (Table II, Panel d). In this study, the use of vaginal misoprostol resulted in a higher success rate than sublingual misoprostol in 24 h, but the abortion rate was similar at 48 h (Table II, Panel d). The findings might be because of the more prolonged effect of vaginal misoprostol on uterine contractility. When pretreatment with mifepristone was given, all women aborted within 24 h of receiving the first dose of misoprostol, and the induction-to-abortion interval for both study groups (vaginal and sublingual) was less than half of that noted in the former study with misoprostol alone (Hamoda *et al.*, 2005a; Tang *et al.*, 2005) (Table II, Panel b). The authors concluded that this effect could be because of prior treatment with mifepristone and the higher initial dose of misoprostol used (Table II, Panel b).

Acceptability was higher in the sublingual group despite the significantly higher rate of side effects. The sublingual route would be the alternative for women who do not like the vaginal route of administration.

Surgical evacuation of the placenta

Routine surgical evacuation of the uterus is not required following mid-trimester medical abortion. It should only be undertaken if there is clinical evidence that the abortion is incomplete (El-Refaey and Templeton, 1995). In recent large case series of mid-trimester medical abortion, only 8–11% of women needed surgical evacuation following medical abortion (Ashok and Templeton, 1999; Tang *et al.*, 2001; Ashok *et al.*, 2004) (Table II, panels a and b). In the latest report from the Scottish group, the rate of surgical evacuation was as low as 2.5% (Hamoda *et al.*, 2005a). These figures thus negate the need to do a routine curettage unless warranted. A very low incidence of surgical evacuation is also consistent with the previous reports (El-Refaey *et al.*, 1993). Complete abortion is achieved with increasing frequency with advancing gestations with >80% occurring at ≥20 weeks (UK Multicenter Study Group, 1997). Performing a routine evacuation, however, does not protect against the need for hospital readmission for post-abortion bleeding and uterine curettage (UK Multicenter Study Group, 1997) (Table II, Panel a). A more

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Table II. Methods of mid-trimester induced abortion

Author	Trial design	Number of subjects, gestational age (weeks)	Regimen		Abortion rate (%)		Mean[§]/Median prostaglandin used	Induction-abortion-interval (h) mean[†]/median	Curettage rate for retained products (%)
			Mifepristone dose/time	Prostaglandins dose/route/time	≤24 h	≤48 h			
Panel a. Mifepristone and gemeprost									
UK Multicenter Study Group (1997)	Open multicenter study (20 centres)	261 (14–26)	600 mg mife orally 36–48 h prior	1 mg geme q3hx5	>93		2 doses	7	53.2
Tang *et al.* (2001)	Case series	956 (12–24)	200 mg mife 36 h prior	1 mg geme q6hx4	96.4	98.8	2 doses	7.8	11.5
Gemzell-Danielsson and Östlund (2000)	Case series	197 (14–26)	600 mg mife 24–48 h prior	1 mg geme q6hx4	96.3		2 doses	9.0 (primi) 7.2 (multi)	Routine curettage for all up to 18th week
Panel b. Mifepristone and Misoprostol different doses and routes									
El-Refaey and Templeton (1995)	Pros RCT	70 (13–20)	600 mg mife 36–48 h prior for both groups	Group 1. (*n* = 35) 600 µg miso vaginally followed by 400 µg q3hx5	97 (24–48 h)		2200 mcg over 12 h well tolerated	6.0	
				group 2. (*n* = 34) 600 µg miso vaginally followed by 400 µg orally q3hx5	97 (24–48 h)			6.7	
Ho *et al.* (1997)	Pros RCT	98 (14–20)	200 mg mife 36–48 h prior for both groups	Vaginal group (*n* = 49) 200 µg miso and placebo q3hx5	73.5		600 mcg	9.0	Nil
				Oral group (*n* = 49) 200 mcg miso and placebo q3hx5	59.2		1000 mcg	13.0	Nil
Ashok and Templeton (1999)	Retrospective	500 (13–21)	200 mg mife 36–48 h prior	800 µg miso vaginally followed by 400 µg orally q3hx4	97.2		1200 mcg	6.5	9.4
Ngai *et al.* (2000)	Pros RCT	142 (14–20)	200 mg mife 36–48 h prior	Group I (*n* = 69) 200 µg miso vaginally q3hx5	84		600 mcg	10.0	24.6
				Group II (*n* = 70) 400 µg miso orally q3hx5	81.4		1200 mcg	10.4	18.6
Ashok *et al.* (2004)	Case series	1002 (13–21)	200 mg mife orally 36–48 h prior	800 µg miso vaginally followed by 400 µg orally q3hx4 in 12 h	97.1	99.2	2.6 (m)[§] 2.8(n)[§]	6.25	8.1
Tang *et al.* (2005)	Pros RCT double blind	120 (12–20)	200 mg mife 36–48 h prior for both groups	Group I (*n* = 58) 400 µg miso sublingually and placebo 2 tabs orally q3hx5	91.4	98.3		5.5	17.2

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Table II. *Continued*

Author	Trial design	Number of subjects, gestational age (weeks)	Regimen		Abortion rate (%)		Mean[§]/Median prostaglandin used	Induction-abortion-interval (h) mean[†]/median	Curettage rate for retained products (%)
			Mifepristone dose/time	Prostaglandins dose/route/time	≤24 h	≤48 h			
				Group II (*n* = 60) 400 µg miso orally placebo 2 tabs sublingually q3hx5	85	91.7		7.5	11.7
Hamoda *et al.* (2005a)	Pros RCT	76 (13–20)	200 mg mife 36–48 h prior for both groups	Vaginal group (*n* = 37) 800 µg miso followed by 400 µg q3hx5			2 doses	5.40	2.5
				Sublingual group (*n* = 32) 600 µg miso followed by 400 µg q3hx5			2 doses	5.27	8.3
Panel c. Mifepristone and prostaglandin analogue									
El-Refaey *et al.* (1993)	Pros RCT	60 (13–20)	600 mg mife 36–48 h prior for both groups	Group 1.(*n* = 30) 400 µg miso orally q3hx3	90			8.0	
				Group 2.(*n* = 30)1 mg geme q3hx5	93			8.3	
Ho *et al.* (1996)	Pros RCT	50 (14–20)	200 mg mife 36–48 h prior for both groups	Group A.(*n* = 25) 400 µg miso orally q3hx5	92			8.7	20
				Group B.(*n* = 25) 1 mug geme q3hx4	88			10.8	40
Bartley and Baird (2002)	RCT	100 (12–20)	200 mg mife 36–48 h prior	Group 1 (*n* = 50) 1 mg gemi q6hx4	96			6.6	12
				Group 2 (*n* = 50) 800 µg miso vaginally followed by 400 µg orally q3hx4	94			6.1	10
Panel d. Prostaglandin analogue alone									
Nuutila *et al.* (1997)	Prospective study	81 (12–24)		Group A (*n* = 27) 100 µg miso vaginally q6hx36x6	74[‡]			23.1[†]	
				Group B (*n* = 26) 200 µg miso vaginally q12hx3	92[‡]			27.8[†]	
				Group C (*n* = 28) 1 mg gemi q3hx3	89			14.5[†]	
Dickinson *et al.* (1998)	Pros RCT double blind	100 (14–28)		1 (*n* = 47) 1 mg gemi q3hx5	75.1			13.7	37.8
				2 (*n* = 53) 200 mcg miso vaginally q6hx4	74.9			16.9	42.5
Wong *et al.* (1998)	Pros RCT	140 (14–20)		Group A (*n* = 70) 1 mg gemi q3hx5	58.6		5 mg	19.0	

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Table II. *Continued*

Author	Trial design	Number of subjects, gestational age (weeks)	Regimen		Abortion rate (%)		Mean[§]/Median prostaglandin used	Induction-abortion-interval (h) mean[†]/median	Curettage rate for retained products (%)
			Mifepristone dose/time	Prostaglandins dose/route/time	≤24 h	≤48 h			
				Group B (*n* = 70) 400 µg miso vaginally and repeated q3hx5	80		1600 mcg	14.1h	
Wong *et al.* (2000)	Pros RCT	148 (15–20)		Group I (*n* = 74) 400 µg miso vaginally q3hx5	73	90.5	2021 mcg[§]	15.2	
				Group II (*n* = 74) 400 µg miso vaginally q6hx3	60.8	75.7*	1546 mcg[§]	19	
Tang *et al.* (2004)	Pros RCT	224 (12–20)		Sublingual group (*n* = 108) 400 µg miso q3hx5	72	91		12.2	17
				Vaginal group (*n* = 112) 400 µg miso q3hx5	86	95		10.5	15
Thong *et al.* (1992)	Retrospectiveanalysis	932 (12–27)		1 mg geme q3hx5	80	90		18 (nulli) 15 (multi)	
Armatage and Luckas (1996)				1 mg geme q3hx5	98[‡]			16	
				1 mg gemeq6hx3	91.8[‡]			15	
Bebbington *et al.* (2002)	Pros RCT	114 Mid-trimester		Oral group,(*n* = 65) 200 µg miso q1h for 3 h followed by 400 µg q4hx6	38.5			34.5[†]	7 pts
				Vaginal group. (*n* = 49) 400 µg q4hx6	85.7			19.6[†]	4 pts
Dickinson and Evans (2002)	Pros RCT DB	150 (14–30)		Group 1.200 µg miso vaginally q6hx48 h	58.8			18.2	24
				Group 2. 400 µg miso vaginally q6hx48 h	76			15.1	42
				Group 1. 600 µg miso followed by 200 mcg q6hx48 h	79.6			13.2	41
Jain *et al.* (1999)	Randomized trial	100 (12–22)		1. (*n* = 47) 200 µg miso vaginally q6hx48 h	80.9	87.2		13.8[†]	
				2. (*n* = 37) 200 µg miso vaginally q12hx48 h	86.5	89.2		14.0[†]	

q3hx5 is every 3 hourly, maximum five doses.
DB, double blind; geme, gemepost; miso, misoprostol; mife, mifepristine; PG, prostaglandin; Pros, prospective; RCT, randomized controlled trial.
*Significant.
†Mean induction-abortion interval.
‡Cumulative abortion rate.
§Mean prostaglandin used.

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determined approach to use surgical evacuation only when indicated would probably reduce the length of hospital admission. For this to be achieved, the use of staff experienced in assessing placental completeness after abortion is essential.

Medical abortion with PG alone

Medical abortion with gemeprost or misoprostol alone has been shown to be effective, although higher doses are needed; side effects are more frequent and the induction-to-abortion interval is longer compared with the combined treatment with mifepristone.

Vaginal application of gemeprost gave an abortion rate of about 88–96.5% in 48 h, and the mean induction-to-abortion interval ranged from 14 to 18 h (Cameron *et al.*, 1987; Thong and Baird, 1992b; Thong *et al.*, 1992; Armatage and Luckas, 1996; Nuutila *et al.*, 1997; Wong *et al.*, 1998) (Table II, Panel d). The main side effects reported were vomiting, diarrhoea and fever (Thong *et al.*, 1992; Nuutila *et al.*, 1997; Wong *et al.*, 1998). The most common regimen studied is 1-mg gemeprost every 3 h for 5 doses in 24 h. It is repeated if abortion does not occur within this time. When 3- and 6-h administration of gemeprost were compared, there was no advantage of 3-h intervals (Armatage and Luckas, 1996) (Table II, Panel d). These results suggest that, by lengthening the interval between insertions of pessaries within the first 24 h, the number of pessaries could be reduced without the loss of clinical efficacy.

Misoprostol has been widely studied in different dosages and routes for the second-trimester TOP (Jain and Mishell, 1994; Nuutila *et al.*, 1997; Wong *et al.*, 2000). Various studies have used doses ranging from 200 to 800 μg at intervals ranging from 3 to 12 h (Jain and Mishell, 1994; Ho *et al.*, 1997; Nuutila *et al.*, 1997; Jain *et al.*, 1999; Ngai *et al.*, 2000; Wong *et al.*, 2000; Bebbington *et al.*, 2002; Dickinson and Evans, 2002). In general, one can expect a similar success rate and induction-to-abortion interval as with gemeprost alone (Table II, Panel d). The misoprostol-only regimen would be of use in those countries where mifepristone is not available. Doses of 600 and 800 μg have shown comparable successful abortion rates but are associated with high rates of fever, diarrhoea, nausea and vomiting (Herabutya *et al.*, 2000, 2001; Pongsatha and Tongsong, 2001). It has been seen that 3-h interval is more effective than 6-h interval (Wong *et al.*, 2000) (Table II, Panel d).

Feticide before late abortion

When medical abortion is chosen, in many settings, clinicians are required to ensure that the fetus is dead at the time of abortion. A legal abortion must not be allowed to result in a live birth and terminations after 21 weeks, the method chosen should ensure that the fetus is not born alive (RCOG, 1996). This is a matter of concern especially for late terminations with or without fetal malformations when one according to local guidelines has to resuscitate if the fetus is born alive. Agents used for feticide are hypertonic saline, 1% lidocaine and potassium chloride (Elimian *et al.*, 1999; Bhide *et al.*, 2002; Senat *et al.*, 2003). Feticide with potassium chloride reduced the PG requirement for mid-trimester medical abortion, compared with similar procedures conducted without feticide (Elimian *et al.*, 1999). Up to 20 weeks of pregnancy, the contractions induced by PG make feticide unnecessary.

Mid-trimester surgical abortion

Vacuum aspiration

VA is the surgical method of choice for first-trimester pregnancy termination. During the procedure, the uterus should be emptied by suction curette and by blunt forceps (if required). This procedure can also be used during the early second trimester. It is generally agreed that the risk of complications increases with gestational age (Brenner and Edelman, 1974). After 8 weeks of gestation, the risk of major complications appears to rise by ~15–30% for each week of delay (Cates *et al.*, 1979). The method of choice at gestations 12–15 weeks depends on the skill and experience of the concerned clinicians. It is well evident from a cohort study that abortion procedures, particularly those at ≥12 weeks, should not be allotted to the most junior staff member (Child *et al.*, 2001). Surgical abortion by conventional suction termination, without the need for specialized instruments, can be undertaken up to 15 weeks of gestation if clinicians have gained experience with this method (RCOG, 2004). The complications could be reduced by preoperative cervical dilatation (Schulz *et al.*, 1983; Grimes *et al.*, 1984). Cervical trauma, the rate of damage to the external cervical os, at the time of surgical abortion is reported to be ~1% [Jacot *et al.*, 1993; Peterson *et al.*, 1983; Schulz *et al.*, 1983; Royal College of General Practioners (RCGP), RCOG, 1985]. The rate is lower when abortions are performed by experienced clinicians and early in pregnancy. The World Health Organization's Technical and Policy Guidance on Safe Abortion and RCOG recommends 'cervical preparation before surgical abortion for durations of pregnancy over 9 weeks for nulliparous women, for women younger than 18 years of age, and for all women with durations of pregnancy more than 10 weeks'. Cervical dilatation can be achieved through mechanical dilatation, laminaria tents, with PG analogues and mifepristone. A large number of studies have proven the safety of PG analogues for cervical dilatation when compared with mechanical dilatation and laminaria tents (Gold *et al.*, 1979; Christensen *et al.*, 1983). The degree of cervical dilatation is related to the duration of treatment. The use of misoprostol/mifepristone has been proven effective for cervical priming before surgical abortion in the first trimester (Urquhart and Templeton, 1990a; Urquhart and Templeton, 1990b; Ngai *et al.*, 1999). In a study by Gottlieb *et al.* (1991), constituting 127 women at 13–14th week of pregnancy, no case of cervical injury or uterine perforation or recurretage was reported, and a post-abortion infection rate of 1.6% was noted. The mean amount of blood loss was 49 ml (range 0–400 ml), and only six patients had blood loss >100 ml. These results were comparable to the same procedure when used in the first trimester without an increased risk, provided the patients were pretreated with PGs.

Dilatation and evacuation

Dilatation and evacuation (D&E) is the standard method at gestations above 13 weeks in many parts of the world. The conventional suction termination would be an appropriate method for gestations between 12 and 15 weeks, whereas D&E would be a safe and an effective option for gestations above 15 weeks when undertaken by specialist practitioners with a sufficient workload to maintain their skills according to RCOG (2004). Although the safety and efficacy of D&E for the termination of mid-trimester pregnancy

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by experienced hands is reassured by the evidence provided (Grimes *et al.*, 1977; Schneider *et al.*, 1996; Autry *et al.*, 2002), some practitioners feel it very distressing to perform this procedure at an advanced gestation. A report on the confidential inquires into the maternal deaths in the UK questioned the appropriateness of D&E as a method of terminating second-trimester pregnancy when safe and effective medical alternatives exist (Report of Confidential Enquires into Maternal Deaths in the United Kingdom, 1994–1996). When D&E was compared to primary PGs, $PGF_{2\alpha}$, D&E was found to be faster, safer and more acceptable up to about 18 weeks of gestation (Grimes *et al.*, 1980). Cervical injury is more frequent with D&E in the second trimester, and hence, preoperative cervical priming reduces the complications (Schulz *et al.*, 1983; Grimes *et al.*, 1984).

Surgical versus medical abortion

Medical abortion at gestations 9–13 weeks has been shown as a safe, acceptable and effective alternative to surgical abortion (Ashok *et al.*, 1998, 2002; Hamoda *et al.*, 2005b). A randomized controlled trial comparing medical abortion with VA at gestations up to 9 weeks showed that, although both the methods were highly acceptable to women, medical abortion was more painful and less effective with advancing gestation (Henshaw *et al.*, 1993, 1994). Since then, the developments of improved regimens including the use of misoprostol has had lot of advantages such as increased efficacy and reduced side effects of medical abortion. Presently, medical abortion is as effective as VA in the late-first and early-second trimester (Ashok *et al.*, 2005a,b).

No randomized study comparing mifepristone and a PG analogue and D&E for mid-trimester abortion has been published. An attempt has been performed, but the trial was stopped after 1 year because of slow enrolment (Grimes *et al.*, 2004). The women declined the method of abortion in each group, and sample size was too small to draw conclusive evidence except for hypothesis generation. In a retrospective cohort study of 297 women, the complication rate of D&E and medical methods for mid-trimester abortion was compared (Autry *et al.*, 2002). The method used for medical abortion was not specified, but in most cases vaginal misoprostol alone was used. The combined treatment with mifepristone was not available. Besides a higher frequency of failed treatment (7 versus 0%) and incomplete abortion (21 versus 0.7%), there were no differences in complication rates. One patient with a history of a previous Caesarean delivery who received misoprostol 200 μg vaginally every 4 h (total dose not reported) had a uterine rupture. There is an increased risk of perforation of the uterus during D&E at advancing gestations. The use of real-time ultrasonography during D&E was reported to reduce the perforation rate. The rate of uterine perforation was 0.2% in the scanned group compared to 1.4% in the unscanned group (Darney and Sweet, 1989). Historically, it has been considered that D&E is a risk factor for subsequent adverse pregnancy outcomes, including cervical incompetence, pregnancy loss and preterm birth. A retrospective case series of 600 women with mid-trimester D&E concluded that 'second trimester D&E is not a risk factor for subsequent mid-trimester pregnancy loss or spontaneous preterm birth' (Kalish *et al.*, 2002). In this study, interpretation of the findings was difficult as no reference cohort of women who had not undergone D&E was described. But still, the rates of pregnancy outcomes appeared similar to those of an unselected population. Thus, D&E can safely be undertaken by gynaecologists who have been trained in the procedure, have the necessary instruments and have a caseload sufficient to maintain their skills. For those lacking the necessary expertise and caseload and for the betterment of their patient's mid-trimester medical abortion, using mifepristone with PG is appropriate. Side effects including nausea, vomiting and diarrhoea are characteristics of PG administration and are because of PG's stimulatory effect on the gastrointestinal tract. Diarrhoea is more common in women using gemeprost, whereas fever is more common with misoprostol (Wong *et al.*, 1996). Serious complications, such as uterine rupture, major haemorrhage and cervical tear, are rare (UK Multicenter Study group, 1997; Gemzell-Danielsson and Östlund, 2000). Uterine rupture cases are reported to occur with both gemeprost and misoprostol, with or without priming by mifepristone (Wiener and Evans, 1990; Norman, 1995; Chen *et al.*, 1999). The incidence of uterine rupture in women without previous scar is estimated to be 0.1–0.2% in the second trimester of pregnancy using mifepristone and gemeprost (Atienza *et al.*, 1980; RCOG, 2004). Major bleeding is usually associated with prolonged retention of the placenta. The drawbacks of medical abortion with older methods such as long duration of labour, hospitalization for several days, need for curettage and invasive administration have been reduced or eliminated when mifepristone and misoprostol (or gemeprost) is used.

There are only few studies reporting regimens for women who do not abort within 24 h. According to some protocols, if abortion does not occur, mifepristone is given followed by repeated vaginal misoprostol (Ashok *et al.*, 2004). Any patient who fails to abort during the second day will get a third dose of mifepristone followed by gemeprost 1 mg every 3 h. There is still insufficient consensus to set a guideline for the failed abortion group of patients, but it could be argued that for women going on to a second or third day, D&E would be a more appropriate approach (Ashok *et al.*, 2004). However, in a later series of 1002 cases with a combination of mifepristone and misoprostol, seven women who failed to abort after the third course eventually aborted using mifepristone and gemeprost (Ashok *et al.*, 2004).

There is a gradual increase in second-trimester abortion because of wide scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities such as cardiovascular and skeletal malformation. In these cases, examination of the fetus could provide valuable information especially after medical abortion to confirm the congenital anomaly and further evaluate the subsequent recurrence risk and provide information to help in counselling of these patients (Boyd *et al.*, 2004).

Day-care abortion

Day-care abortion is recognized as a cost-effective management of service provision. In the era of using older methods for inducing abortion in the second trimester, the majority of women had to be inpatients for a couple of days to achieve abortion. The availability of abortion as a day-care procedure can minimize disruption to the lives of women and their families. The introduction of treatment with mifepristone before mid-trimester abortion with PGs has reduced induction-to-abortion intervals to an extent such that many women undergoing these procedures can be managed as day cases. In a multicenter study performed in 20 hospitals including 267 women, almost 60% of the women aborted within 8 h of PG

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being commenced (UK Multicenter Study Group, 1997). Of the 956 women, 68.6% aborted within 10 h (Tang *et al.*, 2001). In a study of 100 women receiving 200 mg of mifepristone followed 36–48 h later by either gemeprost or misoprostol, >80% of the women aborted the fetus within 12 h in both the groups, confirming that in the majority it is possible to arrange the abortion as a day-care procedure (Bartley and Baird, 2002). In a case series report of 1000 women undergoing mid-trimester abortion with mifepristone followed by misoprostol, over two-thirds were managed as day-cases (Ashok *et al.*, 2004). From these studies, it is suggested that up to 10% of women undergoing induced medical abortion will require inpatient care for medical, social or geographical reasons (or a combination of these).

Pain management

Abdominal pain is one of the most common adverse effects of medical abortion (Spitz *et al.*, 1998; Honkanen *et al.*, 2004). Pain is subjective and difficult to quantify. The amount of pain varies from woman to woman, and it is important to discover what are the factors causing severe pain and what helps to alleviate the pain. Services should make a range of oral and parenteral analgesics available to meet women's needs (RCOG, 2004). In routine clinical practice, analgesia is offered to women following surgical abortion and both during and after medical abortion. However, the analgesia requirements and regimens for medical abortion reported in the literature vary widely (Wiebe, 2001), and there is scant research evidence to select an analgesic regimen and to show the predictors of analgesia (Smith *et al.*, 1979; Westhoff *et al.*, 2000). Analgesic requirement and the perception of pain were significantly higher in women of younger age, longer gestation, those with longer induction-to-abortion interval and with increased number of misoprostol doses (Smith *et al.*, 1979; Belanger *et al.*, 1989; Borgatta and Nickinovich, 1997; Westhoff *et al.*, 2000; Hamoda *et al.*, 2004), whereas the use of analgesia was less in older, parous women and those at shorter gestations (Hamoda *et al.*, 2004). The pain associated with the mid-trimester TOP is probably because of the larger fetus passing through the cervical canal inducing more pain. In a study population of 2049 subjects undergoing first-trimester medical abortion, the variable 'most strongly' ($P < 0.0001$) associated with narcotic use was study center (Westhoff *et al.*, 2000). Further research is needed to evaluate the role of advance or prophylactic analgesia and its effectiveness as well as women's satisfaction and acceptance.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be very effective for treatment of dysmenorrhoea, which is related to intensive uterine contractility (Smith, 1987). They inhibit the production of endogenous PGs, which are important messengers responsible for uterine contractions, cramps and pain sensation. Because treatment with mifepristone increases the endogenous production of PGs that might be of importance for the induced uterine activity (Norman *et al.*, 1991), there has been concern that the use of NSAIDs might attenuate uterine contractility if used for pain treatment during medical abortion. Therefore, such drugs are frequently avoided or recommended against in protocols for medical abortion. However, this recommendation does not seem valid because several studies have shown that the use of NSAIDs did not interfere with the action of misoprostol and/or mifepristone on inducing cervical ripening, uterine contractility (Norman *et al.*, 1991; Creinin and Shulman, 1997; Li *et al.*, 2003) or the time to abortion and expulsion of the products of conception (Fiala *et al.*, 2005).

During suction evacuation or D&E procedure, a majority of the patients experience severe pain. There are usually strong uterine contractions at the end of the suction evacuation procedure, which is when the women are more likely to experience severe cramps and pain. These contractions may last for a few hours, which may lead to post-operative pain. The evacuation pain sensation is a combination of pain because of cervical dilatation and because of uterine contractions. Being simple and easy to administer, a paracervical block (PCB) is accepted as a standard method for local anaesthesia during the procedure. A few randomized control trials have shown that PCB can reduce the pain (Wiebe, 1992; Glantz and Shomento, 2001). The cervix and the lower uterine segment are innervated by parasympathetic fibres from S2 to S4, which form ganglia lateral to the cervix and enter along with the blood vessels. The fundus is innervated by sympathetic fibres from T10 to L1 via the inferior hypogastric nerve, which enters the uterus at the uterosacral ligaments, as well as via the ovarian plexuses that enter at the corna (Paul *et al.*, 1999). By anaesthetizing the nerve plexuses that lie adjacent to the cervix, PCB reduces pain induced by cervical manipulation and dilatation. However, it has less effect on the cramping pain from the fundus of the uterus. Therefore, PCB alone is not effective for pain relief after cervical priming with misoprostol and use of intravenous sedation is needed regardless of whether the local anaesthetic was injected into the cervix or vaginal vault (Kan *et al.*, 2004). Research into other methods of pain relief and conscious sedation may be helpful to further enhance patient satisfaction.

Midtrimestrer induced abortion and prior CS

There have been increasing CS rates over the past few years, more so because of the increasing use of prenatal diagnosis, one child norm, HIV and improved fetal survivability. The present CS delivery rate is 24.4% in USA, and it is generally increasing worldwide. CS delivery is now the most frequent major surgical procedure performed in the field of obstetrics and gynaecology. Although many studies have demonstrated the small risk of complications for vaginal birth at term after a prior CS (Miller *et al.*, 1994) and the safety of early medical abortion (Gao and Wang, 1999; Xu *et al.*, 2001; Gautam and Agrawal, 2003), the experience of a mid-trimester pregnancy termination in women with prior uterine scar is more limited (Rosen *et al.*, 1991) (Table III). Uterine rupture, haemorrhage and hysterotomy/hysterectomy remain uncommon and inevitable complications of any termination method used in second-trimester pregnancy. As per the literature review, it seems that uterine rupture is associated with the use of intravenous high-dose oxytocin (Atienza *et al.*, 1980). Three small case series of 87 women with at least one CS undergoing second-trimester pregnancy termination with misoprostol reported no case of uterine rupture (Herabutya *et al.*, 2003; Pongsatha and Tongsong, 2003; Rouzi, 2003) (Table III). The retrospective case series of 606 cases using PGE_2, concentrated oxytocin and dilute oxytocin reported an increased incidence of uterine rupture and need for blood transfusion in women with prior CS delivery (Chapman *et al.*, 1996) (Table III). There was no increased risk of complications when 101 patients with a prior CS were compared with 619 women with an unscarred uterus (Dickinson, 2005). In a cohort

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Table III. Mid-trimester induced abortion and prior Caesarean section

Author	Trial design	Total number of subjects, Gestational age (weeks)	Categories	Regimen	Abortion rate (%) ≤24 h	Induction–abortion interval median	Blood transfusion	Uterine rupture	Curettage for retained products
Chapman *et al.* (1996)	Retrospective	606 (11–28)	No prior CS (n = 527)	PGE_2, oxytocin, PGF2α			5.3%	0.2%	25.4%
			Prior CS (n = 79)				11.4%*	3.8%	26.6%
Dickinson (2005)	Case series	720 (14–28)	No prior CS (n = 619)	Misoprostol	76.1	16.6	1.9%	0	34.4%
			Prior CS (n = 101)		82.2	14.5	4.0%	0	41.6%
Daskalakis *et al.* (2005)	Retrospective	324 (17–24)	No prior CS (n = 216)	Misoprostol	70.8	18	7 pts	1	12 pts (5.5%)
			Prior CS (n = 108)		65.7	19	2 pts	0	9 pts (8.3%)
Herabutya *et al.* (2003)	Prospective cohort study	593 (14–26)	No prior CS (n = 528)	Misoprostol		15.8	1	0	
			Prior CS (n = 56)			15.1	0	0	
Pongsatha and Tongsong (2003)	Case series	247 second trimester	No prior CS (n = 226)	Misoprostol				0	
			Prior CS (n = 21)					0	

*Statistically significant.

study, similar result of blood loss >500 ml was seen as reported in the Chapman study (Herabutya *et al.*, 2003). Among 23 women with a history of CS treated with the combination of mifepristone and gemeprost, one case of asymptomatic uterine rupture was reported (Boulot *et al.*, 1993). In addition, there are case reports of uterine rupture with the use of misoprostol in the scarred uterus (Chen *et al.*, 1999; Berghahn *et al.*, 2001). It could be speculated that, with the combination of mifepristone and misoprostol, the incidence of uterine rupture should be lower because of the advantage of cervical dilatation facilitated by mifepristone even before the uterus begins to contract to expel its contents. More studies are needed to evaluate the optimal mifepristone and misoprostol combination in women with prior CS.

Conclusions

Treatment with mifepristone–misoprostol is a safe and an effective method for mid-trimester medical abortion. In most patients, routine surgical evacuation of the placenta is not necessary. More studies are required to compare the medical methods to surgical ones. Patients with prior CS undergoing medical abortion need to be managed more carefully for the early detection of impending complications. Further studies are needed to confirm the safety of medical regimens in these patients.

Women should be offered analgesics whenever required. Studies should focus on improving pain management. Medical abortion is advantageous with regard to evaluation of the fetus and placenta in cases of fetal malformation. This would help in future research practice for betterment of complicated pregnancies. Further studies are also needed on the treatment of women with failed medical abortion after 24 h.

Current recommendations

(i) Cervical priming is mandatory before mid-trimester surgical abortion.

(ii) Misoprostol 400 μg (2 × 200 μg tablets) vaginally 3 h before surgery.

(iii) Gemeprost 1 mg vaginally 3 h before surgery.

(iv) Mifepristone 200 mg orally 12–48 h before surgery.

(v) The treatment may need to be repeated or the interval may be increased in late second-trimester abortions.

Mid-trimester surgical abortion

(i) VA can be carried out up to 15 weeks gestation preceded by cervical priming.

(ii) D&E can be used by trained and skilled providers with sufficient experience.

Mid-trimester medical abortion

(i) Mifepristone 200 mg orally, followed 24–48 h later by misoprostol 800 μg vaginally and thereafter by repeated doses of misoprostol 400 μg orally, every 3 h, to a maximum of four oral doses.

(ii) Mifepristone 200 mg orally, followed 24–48 h later by gemeprost 1 mg vaginally every 6 h to a maximum of five pessaries.

(iii) Misoprostol only regimens (in countries where mifepristone is not available); vaginal misoprostol 800 μg every 12 h.

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(iv) Mid-trimester TOP in prior CS patients should be carried out with caution.

(v) Routine surgical evacuation of the uterus following medical abortion is not required.

(vi) Analgesics should be offered to all women when required.

(vii) Vaginal misoprostol or gemeprost can be administered either by the woman or by a clinician according to the preference of the woman.

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