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Second Trimester Medical Abortion with Mifepristone–Misoprostol and Misoprostol Alone: A Review of Methods and Management

Kristina Gemzell-Danielsson,^a Sujata Lalitkumar^b

Abstract: Second trimester abortions constitute 10–15% of all induced abortions worldwide but are responsible for two-thirds of major abortion-related complications. During the last decade, medical methods for second trimester induced abortion have been considerably improved and become safe and more accessible. Today, in most cases, safe and efficient medical abortion services can be offered or improved by minor changes in existing health care facilities. Second trimester medical abortion can be provided by a nurse-midwife with the back-up of a gynaecologist. Because of the potential for heavy vaginal bleeding and serious complications, it is advisable that second trimester terminations take place in a health care facility where blood transfusion and emergency surgery (including laparotomy) are available. This article provides basic information on regimens recommended for second trimester medical abortion. The combination of mifepristone and misoprostol is now an established and highly effective method for second trimester abortion. Where mifepristone is not available or affordable, misoprostol alone has also been shown to be effective, although a higher total dose is needed and efficacy is lower than for the combined regimen. Therefore, whenever possible, the combined regimen should be used. Efforts should be made to reduce unnecessary surgical evacuation of the uterus after expulsion of the fetus. Future studies should focus on improving pain management, the treatment of women with failed medical abortion after 24 hours, and the safety of medical abortion regimens in women with a previous caesarean section or uterine scar. ©2008 Reproductive Health Matters. All rights reserved.

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A LTHOUGH the majority of abortions are performed in the first trimester, there is still a need for second trimester abortion because of delayed diagnosis of fetal anomalies, logistic and financial difficulties in obtaining abortion services, and failure to recognise an undesired pregnancy in the first trimester, which all contribute to the continuing need for late abortions.^{1,2}

Second trimester abortions constitute 10–15% of all induced abortions worldwide but are respon-

sible for two-thirds of all major abortion-related complications. Medical abortion, the termination of pregnancy through the use of a drug or a combination of drugs, has the potential to reduce complications and to expand access to abortion provided not only by specially trained clinicians but also by other health care providers who may or may not have training in surgical methods of abortion. Today, in most cases, safe and efficient medical abortion services can be offered or

a Professor, Department of Woman and Child Health, Division of Obstetrics and Gynaecology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden. E-mail: kristina.gemzell@ki.se

b Specialist in Obstetrics and Gynaecology, Department of Woman and Child Health, Division of Obstetrics and Gynaecology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

improved by minor changes in existing health care facilities. This article aims to provide basic information on regimens recommended for second trimester medical abortion and best practice in management.

Development and use of medical abortion

Different surgical and medical methods of abortion have been used since ancient times. Surgical abortion is one of the oldest and most commonly practised techniques in many parts of the world. A matter of great concern in the past was that there were no safe drugs for inducing an abortion. Women have used various herbs. salts, douches and purgatives, all with questionable success to achieve pregnancy termination.³ Among the methods listed as outdated by WHO. but still commonly used in several developing countries (e.g. India, China and until recently Mongolia), is intra- or extra-amniotic administration of ethacryidine lactate (Rivanol), especially to terminate late second trimester pregnancies.⁴ The drawbacks of older methods include long duration of labour, hospitalisation for several days and the need for curettage. In recent years, effective medical abortion methods with low morbidity have emerged and are becoming more accessible. With the introduction of prostaglandins and later prostaglandin analogues, the efficacy of medical abortion could be improved, and the risk of complications and side effects reduced. Medically induced abortion was further improved when mifepristone became available in the 1980s.5-9 With mifepristone, the induction-to-abortion interval was shortened, and the dose of prostaglandin analogues required (and thus side effects) was reduced. Today, medical abortion is the method of choice in many centres.¹⁰

Medical abortion during early pregnancy was first approved in France in 1988 (up to 49 days of amenorrhoea) followed by approval in the UK (1991) and Sweden (1992) (up to 63 days of amenorrhoea in both the countries). A few years later approval followed in these countries for second trimester medical abortion. However, it was only in 1999–2000 that both early first and second trimester medical abortion with mifepristone and a prostaglandin analogue were approved in several other European countries.

The optimal method of second trimester abortion continues to be debated. This is an important

question because of the disproportionate amount of abortion-related morbidity and mortality with second trimester terminations, especially with older methods.^{4,11} Today, dilation and evacuation (D&E) is the standard method of second trimester surgical abortion in many parts of the world. In the United States, in 2000, D&E was used for 99% of abortions between 13-15 weeks. 95% between 16-20 weeks and 85% at 21 weeks or later.¹² In England and Wales, D&E has also been the main method of second trimester abortion: however, medical abortion is more common than in the US and is increasingly being used. In contrast, medical abortion is the standard method for second trimester abortion in the Scandinavian and Nordic countries since the introduction of the combined mifepristone-prostaglandin regimen. In many other European countries, second trimester abortions due to fetal abnormalities are also performed using medical methods. There is a gradual increase in second trimester abortion in some European countries because of wide-scale introduction of antenatal screening programmes to detect fetal abnormalities such as an encephaly and cardiovascular and skeletal malformations. In these cases, examination of the fetus could provide valuable information, which medical abortion allows, to confirm the congenital anomaly, further evaluate the subsequent risk of recurrence and provide information to help in counselling of these patients.¹³

Who can provide second trimester abortion?

Specialised training and a sufficient workload to maintain the skills, as well as special instruments, are required to perform D&E safely according to the World Health Organization (WHO) and the Roval College of Obstetricians & Gynaecologists (RCOG).^{14,15} Although the evidence shows the safety and efficacy of D&E in experienced hands,^{16,17} some practitioners find it distressing to perform this procedure at an advanced gestation. Furthermore, a report on the confidential inquires into maternal deaths in the UK guestioned the appropriateness of D&E for second trimester abortion when safe and effective medical alternatives exist.¹⁸ In the Scandinavian countries, the use of second trimester medical abortion assures wide access to induced abortion since it can be performed in all gynaecological clinics. Furthermore, in these settings mid-level providers with adequate training and back-up can provide the abortion care. Because of the potential for heavy vaginal bleeding and serious complications in a small number of women, however, it is advisable for second trimester terminations to take place in health care facilities where gynaecologists, blood transfusion and access to emergency surgery (including laparotomy) are available.

Drugs used for medical abortion

For abortion at 13–24 weeks of gestation, medical abortion with mifepristone followed by a prostaglandin (PG) analogue is an appropriate method and has been shown to be safe and effective.^{15,19,20} The combination of mifepristone and misoprostol has synergistic effects and stimulates expulsion of the pregnancy.

The most commonly used combination is:

- mifepristone, taken first
- misoprostol, 24-48 hours later

Mifepristone is the only antiprogestin approved for the induction of abortion. It is a 19norsteroid, which binds with high affinity to the progesterone receptor, thus inhibiting the effect of progesterone. Progesterone is a key hormone in maintaining pregnancy by keeping the uterus in a quiescent state. It prevents softening and dilatation of the cervix, reduces PG output from the decidua and suppresses uterine contractions. Thus, the blocking of progesterone receptors by mifepristone results in vascular damage, decidual necrosis and bleeding,^{8,21} which leads to cervical softening, increased uterine sensitivity to PG and conversion of the quiet pregnant uterus into an organ of spontaneous activity with maximal effect at 36-48 hours.^{8,9,22,23}

Misoprostol is a synthetic PGE-1 analogue which induces cervical ripening as well as strong uterine contractions and leads to expulsion of a pregnancy. Prostaglandins play an important role in the regulation of uterine contractility during pregnancy.²⁴ The receptors are present throughout the pregnancy; hence, PGs and PG analogues are effective for termination of pregnancy. Misoprostol has been shown to have several advantages over other prostaglandins; it is cheap, stable at room temperature and can be stored for a long time. Misoprostol is equally or more effective compared with the PG analogue gemeprost.^{25,26} The oral tablet is effective in different routes of administration and the dose of prostaglandin can be easily adjusted according to need. In contrast to other prostaglandins, misoprostol has limited effect in the bronchi or blood vessels. Side effects are dose dependent, usually mild and self-limiting.²⁷

Indications and usage

Although in most countries mifepristone followed by a prostaglandin analogue is approved for medical termination of early first trimester pregnancy (Mifepristone, Exelgyn, Paris, France), mifepristone with repeated doses of a prostaglandin analogue (most commonly misoprostol) is also licensed and widely used for abortion of later pregnancies. Studies carried out in many different countries provide evidence of the safety of medical abortion up to 24 weeks of pregnancy.¹⁹

However, it should be noted that while the dose of mifepristone does not change, the dose of misoprostol needs to be modified according to gestational age. A higher total dose is often needed in the late first trimester compared to the early first trimester. During the second trimester, due to increased sensitivity of the uterine muscles to PGs, lower doses are sufficient. One needs to be very vigilant about hyperstimulation and uterine rupture in cases with previous caesarean section or any uterine scar in pregnancies beyond 20 weeks.

Contraindications

Absolute contradictions

There are very few absolute contraindications to medical abortion. When using a combination of mifepristone and misoprostol they include:

- Known or suspected ectopic pregnancy
- Previous allergic reaction to any of the drugs
- Inherited porphyria
- Chronic adrenal failure
- Haemorrhagic (coagulation) disorder

Caution

Caution is required if the woman:

- is on corticosteroid therapy
- has severe anaemia
- has pre-existing heart disease or cardiovascular risk factors.

Safety; avoiding delays

It should be remembered that complications and side effects with medical abortion increase with increasing length of pregnancy. To reduce such complications abortion should be performed as early as possible without unnecessary delay; health care professionals should receive adequate training; and back-up services, including uterine evacuation and blood transfusion, should be available.

Regimens: current recommendations based on the available evidence

Mifepristone and misoprostol act synergistically in combination, and where both are available both should be used. Misoprostol alone should be used in countries where mifepristone is not available. As with early medical abortion, the goal has been to find a regimen combining the lowest doses of both drugs that is highly effective and has the fewest side effects, and which is also acceptable for women.

For second trimester abortion (13–24 weeks of gestation), medical abortion with mifepristone followed by a PG analogue is an appropriate method and has been shown to be safe and effective, according to WHO and the RCOG.^{15,20} It has been well proven that pre-treatment with mifepristone 24–48 h before PG administration increases the success rate, shortens the induction-to-abortion interval and reduces the amount of PGs required in the second trimester.^{28–30}

Second trimester abortion in prior caesarean section patients should be carried out with caution.

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

Analgesics should be offered to all women when required.

Vaginal misoprostol or gemeprost can be administered either by the woman herself or by a clinician, according to the preference of the woman.

Mifepristone-misoprostol regimen

• Mifepristone 200 mg orally, followed 36-48 hours later by misoprostol 800 micrograms vaginally and thereafter by repeated doses of 400 micrograms misoprostol orally, every 3 hours, to a maximum of 4 oral doses.

The combined regimen of mifepristone and misoprostol has an abortion rate as high as 97% and the median induction-to-abortion interval

is as low as 6.0 hours.³¹ The effect of misoprostol is dependent on the route of administration. Vaginal misoprostol is more effective and has fewer side effects, but it may be less acceptable to some women. The sublingual route has therefore been investigated and shown to be convenient and acceptable although slightly less effective.^{27,30,32–34}

Interval between mifepristone and misoprostol: Maximal priming effect on the myometrium is achieved 36–48 hours after pre-treatment with mifepristone. A shorter interval of 24 hours resulted in a slightly longer induction-to-abortion interval, a higher total dose of misoprostol used and a higher rate of uterine curettage (p<0.001).³⁵ Similarly, retrospective data comparing 24– and 48-hour intervals showed that when the interval was reduced to 24 hours, the induction-to abortion interval was longer (9.8 hours vs. 7.5 hours) (p<0.01).³⁶ As both of these studies report significantly longer induction times, the 36–48 hour administration interval may be preferable if practical for services.

About 0.2–0.4% of women abort with mifepristone only. 37,38

Misoprostol-alone regimen: if mifepristone is not available

• Vaginal misoprostol 400 micrograms, every 3 hours, to a maximum of 5 vaginal doses.

In countries where mifepristone is not available or affordable, gemeprost or misoprostol alone have been shown to be effective, although a higher total dose is needed and is less effective than the combined regimens.^{30,32,39–45} The induction-to-abortion interval, 10–15 hours, is longer than with the combined treatment with mifepristone. Since a higher dose is required, the abortion process may have more side effects, such as nausea, vomiting, abdominal pain, fever and shivering.^{46–48} There is also a higher rate of failed abortion and continuing live pregnancy. With the misoprostol alone regimen, 80–90% of women will abort within 24 hours.^{42,45,48}

A meta-analysis of randomised trials comparing gemeprost with misoprostol (using various dosage regimens of misoprostol) showed that vaginal misoprostol compared with gemeprost was associated with a reduced need for narcotic analgesia and surgical evacuation of the uterus.⁴⁹ When a regimen of 400 micrograms of vaginal misoprostol every 3 hours was compared with 1 mg of gemeprost every 3 hours, the inductionto-abortion interval was significantly shorter in the vaginal misoprostol group.⁴² Many misoprostolalone regimens have been reported in the literature with good results. Most of the trials were conducted in pregnancies of 13–22 weeks. For this gestational period, a regimen of 400 micrograms of vaginal misoprostol every 3 hours up to 5 doses is recommended, as it appears to be effective without excessive side effects or complications.⁵⁰

Mifepristone-gemeprost regimen: going out of use

• Mifepristone 200 mg orally, followed 24– 48 hours later by gemeprost 1 mg vaginally every 6 hours to a maximum of five pessaries.

Gemeprost was the standard PG analogue in medical abortion and cervical priming until misoprostol became available.⁵¹ Vaginal gemeprost-only regimens have an abortion rate of 88-96.5% with a longer induction-to-abortion interval compared to the combined regimen. With pre-treatment with mifepristone, the abortion rate in 24 hours was increased from 72% to 95%,⁵² the induction-to-abortion interval was reduced from 15.7 to 6.6 hours and the PG dose was also reduced without loss of clinical efficacy with much reduced side effects.^{52,53} Although shown to be highly effective, gemeprost has several disadvantages compared with misoprostol (i.e. cost and the need for refrigeration limits its usage in developing countries), which has led to misoprostol replacing gemeprost for all indications.

Pain management

Abdominal pain is one of the most common adverse effects of medical abortion.⁵⁴ In routine clinical practice, analgesia should be offered to all women. The perception of pain and request for pain relief has wide individual and cultural variations. Services should make a range of oral and parenteral analgesics available to meet women's needs.¹⁵ Pain is most likely to be felt in the first few hours after PG analogue administration. Studies have shown that analgesic requirement and the perception of pain are significantly higher in women of younger age and those at a higher gestational age, with a longer induction-to-abortion interval and with a greater

number of misoprostol doses, whereas it is less in older, parous women and those at lower gestations.⁵⁵ However, none of these factors is sufficiently predictive to be useful in the management of individual cases. Non-steroidal antiinflammatory drugs (NSAIDs) are a potential first-line treatment. They inhibit the production of endogenous PGs which are important messengers responsible for uterine contractions, cramps and pain sensation. NSAIDs do not interfere with the action of misoprostol and/ or mifepristone on inducing cervical ripening, uterine contractility^{22,56,57} or the time to abortion and expulsion of the products of conception.58 The role of advance or prophylactic analgesia. conscious sedation and para-cervical block and their effectiveness, as well as women's satisfaction and acceptance, need further research.

Side effects and complications

Side effects, including nausea, vomiting and diarrhoea, are characteristics of PG administration and are caused by PG's stimulatory effect on the gastrointestinal tract. Diarrhoea is more common in women using gemeprost, whereas fever is more common with misoprostol.45 Serious complications, such as uterine rupture, major haemorrhage and cervical tear, are rare.^{40,59} Uterine rupture cases are reported to occur with both gemeprost and misoprostol, with or without priming by mifepristone.^{60–62} 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.^{15,63} Major bleeding is usually associated with prolonged retention of the placenta. Heavy bleeding requiring transfusion has been reported in less than 1% of women. 40,54,59 Infection may occur with any induced abortion. About 3% of women required antibiotic treatment because of suspected infections in a large series of over 1,000 women who had a second trimester abortion.59

Feticide before abortion after 21 weeks of pregnancy

When medical abortion is chosen, in many settings, clinicians are legally required to ensure that the fetus is dead at the time of abortion. According to the RCOG, a legal abortion must not be allowed to result in a live birth, and at terminations after 21 weeks, the method chosen should ensure that the fetus is not alive.⁶⁴ This is especially important for late terminations (with or without fetal malformation) if policy requires the provider to resuscitate if the fetus is born alive.

Agents used for feticide are hypertonic saline, 1% lidocaine and potassium chloride or intraamniotic digoxin (1–1.5 mg).^{65–68} Up through 21 weeks of pregnancy, the contractions induced by PG make feticide unnecessary.

Day-care abortion

Dav-care abortion is recognised as a patientcentred and cost-effective form of service provision. In the era of older methods for inducing second trimester abortion, a 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 minimise disruption to the lives of women and their families. The introduction of mifepristone treatment prior to PG analogue has reduced induction-to-abortion intervals sufficiently such that many women (more than 75%) undergoing these procedures can be managed as day cases. With the regimen of a combination of mifepristone and vaginal misoprostol, as described above, the median inductionto-abortion interval is 5.9-6.6 hours.^{26,40,41,59}

Regimens for delayed expulsion

There are only a few studies reporting regimens for women who do not abort within 24 hours. According to some protocols, if abortion does not occur, mifepristone is given again, followed by repeated vaginal misoprostol.⁵⁹ Any patient who fails to abort during the second day would get a third dose of mifepristone followed by gemeprost 1 mg every 3 hours. There is still insufficient consensus to set a guideline for the failed or delayed group of abortion 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.⁵⁹ If a choice is available, the women should decide which way to proceed.

Surgical evacuation of the placenta

Routine surgical evacuation of the uterus is not required following second trimester medical abortion. It should only be undertaken if there is clinical evidence that the abortion is incomplete.¹⁵

After the fetus is aborted, the placenta is usually expelled within a short time. An injection of oxytocin may be given to help the expulsion of the placenta. If the placenta is not delivered within 1–2 hours, an infusion of 10 units oxytocin in 500 ml of normal saline at a rate of 20– 30 drops/min may be given to help the expulsion of the placenta or other uterotonic drugs according to local guidelines.^{15,53} After expulsion, the placenta should be examined to see whether it is complete. If the placenta is incomplete, evacuation of the uterus may be needed. If the placenta is not delivered after more than 1–2 hours observation, or the woman starts bleeding excessively, evacuation of the uterus may be required.

After abortion, the woman should be observed in the hospital for at least 4 hours to monitor the vital signs and the amount of vaginal bleeding. If there is heavy vaginal bleeding, a careful speculum and pelvic examination should be performed to exclude the possibility of lacerations of the cervix. If there is no evidence of lacerations in the lower genital tract but the uterus is not contracting well and the bleeding persists, the uterine cavity should be explored to see whether there are any retained products of conception.

In recent large case series of second trimester abortion only 2.5–11% of women needed surgical evacuation following medical abortion.^{36,41,59,69} Complete abortion is achieved with increasing frequency with advancing gestation.⁴⁰ Performing a routine evacuation, however, does not protect against the need for hospital readmission for post-abortion bleeding and uterine curettage. A more determined approach – using surgical evacuation only when needed – can be practised by training staff in assessing placental completeness after abortion.

Second trimester abortion and prior caesarean section

The caesarean section rate is generally increasing worldwide. Although many studies have demonstrated the small risk of complications for vaginal birth at term after a prior caesarean section, experience with second trimester abortion in women with prior uterine scar is limited.^{70,71} Uterine rupture, haemorrhage and hysterotomy/ hysterectomy remain uncommon but are possible complications of any second trimester termination method used. A literature review found that uterine rupture is associated with the use of high dose oxytocin.⁶³ Among 23 women with a history of prior caesarean section treated with the combination of mifepristone and gemeprost, one case of asymptomatic uterine rupture was reported.⁷² In addition, there are case reports of uterine rupture with the use of misoprostol in the scarred uterus.^{61,73}

Pre-abortion management

Counselling

Both counselling and abortion should be provided without undue delay. Women should be free to choose to be counselled alone or with a partner, parent or friend. Ideally, pre-abortion counselling should also include contraceptive counselling and provision, making it possible to begin the chosen method of contraception immediately after the abortion.

Physical examination and ultrasound scan

In most cases, pregnancy is confirmed and its length estimated on the basis of the woman's history and physical examination. Ultrasound examination is not necessary in the majority of women, although commonly used. It may be helpful to use ultrasound to diagnose pathologies or a nonviable pregnancy.

Clinical assessment and laboratory investigations

A clinical history should be obtained to identify contraindications and risk factors for complications. History of a patient should include personal and family history of relevant diseases; current use of any medications, allergies; obstetric and gynaecological history; any bleeding tendencies; and history of sexual transmitted infections. Social history should include a risk assessment for sexually transmitted diseases, taking into account local prevalence rates. Any genital infection should be excluded or treatment started prior to the abortion. The clinician must be alert to the possibility of violence or coercion in the context of the unwanted pregnancy.

Vital signs like pulse, blood pressure and temperature should be recorded at baseline and during treatment. Haemoglobin level, blood group and Rhesus (Rh) typing should be determined. Rh-negative women should receive anti-D prophylaxis.

The abortion procedure

Treatment with mifepristone and misoprostol typically involves two visits to the clinic by a woman for pregnancy above nine weeks.¹⁵ It may also include a follow-up visit a few weeks after the abortion.

First visit

A single 200 mg tablet of mifepristone is taken orally. The woman is advised to return after 36– 48 hours for day-care admission to complete the abortion procedure with misoprostol. It is very seldom that women abort with mifepristone (0.2–0.4% of cases), but the woman should be informed that this may occur. She should also be informed regarding expected effects of the drugs and possible side effects. In case of significant bleeding and/or contractions the woman should be advised to come to the clinic.

Second visit

During the second visit the woman is admitted to the clinic for misoprostol administration. An initial dose of 800 micrograms vaginally followed by 400 micrograms orally every 3 hours, to a maximum of 4 oral doses, is administered. Appropriate pain relief should be given during the abortion. Abortion may take place after any of the doses of misoprostol. After expulsion, the placenta should be examined to see whether it is complete. If the placenta is incomplete, evacuation of the uterus may be needed.

The woman is kept under observation for at least 4 hours after the expulsion to monitor the vital signs and the amount of vaginal bleeding. At discharge from the clinic, women should be informed regarding expected effects and possible side effects or complications.

From 15 weeks of pregnancy onwards, lactation inhibition medication should be given.

Expected effects and side effects

Most women develop abdominal cramps and start bleeding after the administration of misoprostol. Usually the amount of bleeding is not excessive. The cramps are due to uterine contractions, which are needed to abort the pregnancy. Appropriate information and pain medication allow the woman to relax, which reduces discomfort. NSAIDs for pain relief can be given together with misoprostol. Some women may require narcotic analgesics or a para-cervical block for pain relief.

If needed the woman may be given antiemetics. Fever and chills are fairly common after administration of misoprostol. These do not indicate that the woman has an infection. Antipyretics may be given if necessary. These side effects usually subside or resolve 24 hours after the last dose of misoprostol.

Future studies

Future 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 to develop better ways to deal with complicated pregnancies. Further studies are also needed on the treatment of women with failed medical abortion after 24 hours. There is also a need to further reduce unnecessary surgical evacuation of the uterus after expulsion of the fetus and for guidelines on regimens to help the expulsion of the placenta. More studies are also needed to evaluate the optimal combination of mifepristone and misoprostol in women with prior caesarean section.

References

- Drey EA, Foster DG, Jackson RA, et al. Risk factors associated with presenting for abortion in the second trimester. Obstetrics & Gynecology 2006;107(1): 128–35.
- Grimes DA. The continuing need for late abortions. JAMA 1998; 280(8):747–50.
- Bujalkova M. Birth control in antiquity. Bratisl Lek Listy 2007; 108(3):163–66.
- Medical Methods for Termination of Pregnancy. WHO Technical Report Series 871. World Health Organization, Geneva, 1997.
- Urquhart DR, Templeton AA. Mifepristone (RU 486) and second-trimester termination. Lancet 1987;2(8572):1405.
- Silvestre L, Dubois C, Renault M, et al. Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue. A large-scale French experience. New England Journal of Medicine 1990;322 (10):645–48.
- Gottlieb C, Bygdeman M. The use of antiprogestin (RU 486) for termination of second trimester pregnancy. Acta Obstetrica et Gynecologica Scandinavica 1991;70(3):199–203.
- 8. Bygdeman M, Swahn ML. Progesterone receptor blockage. Effect on uterine contractility

and early pregnancy. Contraception 1985 Jul;32(1): 45–51.

- Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. British Journal of Obstetrics & Gynaecology 1988; 95(2):126–34.
- Royal College of Obstetricians and Gynaecologists. Induced Abortion Guidelines No.11. London: RCOG, 1997.
- Bartlett LA, Berg CJ, Shulman HB, et al. Risk factors for legal induced abortion-related mortality in the United States. Obstetrics & Gynecology 2004; 103(4):729–37.
- Elam-Evans LD, Strauss LT, Herndon J, et al. Abortion surveillance - United States, 2000. Morbidity and Mortality Weekly Report Surveillance Summaries 2003;52(12):1–32.
- Boyd PA, Tondi F, Hicks NR, et al. Autopsy after termination of pregnancy for fetal anomaly: retrospective cohort study. BMJ 2004;328(7432):137.
- Safe Abortion: Technical and Policy Guidelines for Health Systems. Geneva: World Health Organization, 2003.
- 15. Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced

Abortion. Guidelines No.7. London, 2004.

- Grimes DA, Schulz KF, Cates W, Jr., et al. Mid-trimester abortion by dilatation and evacuation: a safe and practical alternative. New England Journal of Medicine 1977;296(20):1141–45.
- Autry AM, Hayes EC, Jacobson GF, et al. A comparison of medical induction and dilation and evacuation for secondtrimester abortion. American Journal of Obstetrics & Gynecology. 2002;187(2):393–97.
- Report of Confidential Enquires into Maternal Deaths in the United Kingdom (1994–1996) Why Mothers Die. Department of Health. London: Her Majesty's Stationary Office. 1997.
- Lalitkumar S, Bygdeman M, Gemzell-Danielsson K. Mid-trimester induced abortion: a review. Human Reproduction Update. 2007;13(1):37–52.
- 20. World Health Organization. Unsafe Abortion: Global Estimates of the Incidence of Unsafe Abortion and Associated Mortality in 2000. 4th ed. Geneva: WHO, 2004.
- 21. Johannisson E, Oberholzer M, Swahn ML, et al. Vascular changes in the human endometrium following the administration of the progesterone antagonist RU 486.

Contraception 1989;39(1): 103–17.

- Norman JE, Thong KJ, Baird DT. Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. Lancet 1991;338 (8777):1233–36.
- 23. Radestad A, Christensen NJ, Stromberg L. Induced cervical ripening with Mifepristone in first trimester abortion. A doubleblind randomized biomechanical study. Contraception 1988;38(3): 301–12.
- Mitchell MD. Regulation of eicasanoid biosynthesis during pregnancy and parturition. In: Hiller K, editor. Eicsanoids and Reproduction. Lancaster: MTP Press, 1987. p.108–27.
- 25. Ho PC, Chan YF, Lau W. Misoprostol is as effective as gemeprost in termination of second trimester pregnancy when combined with mifepristone: a randomised comparative trial. Contraception 1996;53(5):281–83.
- 26. Bartley J, Baird DT. A randomised study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. BJOG 2002;109(11):1290–94.
- 27. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. International Journal of Gynecology & Obstetrics 2007;99(Suppl 2): S160-67.
- Thong KJ, Baird DT. A study of gemeprost alone, dilapan or mifepristone in combination with gemeprost for the termination of second trimester pregnancy. Contraception 1992; 46(1):11–17.
- 29. Ho PC, Tsang SS, Ma HK. Reducing the induction to abortion interval in termination of second trimester pregnancies: a comparison of mifepristone with laminaria tent. British Journal of

Obstetrics & Gynaecology 1995; 102(8):648–51.

- 30. Ho PC, Ngai SW, Liu KL, et al. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstetrics and Gynecology 1995;102(8):648–51.
- 31. el-Refaey H, Templeton A. Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimens. Human Reproduction 1995;10(2):475–78.
- 32. Ngai SW, Tang OS, Ho PC. Randomized comparison of vaginal (200 microg every 3 h) and oral (400 microg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. Human Reproduction 2000; 15(10):2205–08.
- 33. Hamoda H, Ashok PW, Flett GM, et al. A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. Human Reproduction 2005;20(8):2348–54.
- 34. Tang OS, Lau WN, Chan CC, et al. A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. BJOG 2004;111(9): 1001–05.
- 35. Heikinheimo O, Suhonen S, Haukkamaa M. One- and 2-day mifepristone-misoprostol intervals are both effective in medical termination of second-trimester pregnancy. Reproductive BioMedicine Online 2004;8(2):236–39.
- 36. Nilas L, Glavind-Kristensen M, Vejborg T, et al. One or two day mifepristone-misoprostol interval for second trimester abortion. Acta Obstetricia et Gynecologica Scandinavica 2007;86(9):1117–21.
- 37. UK Multicentre Study Group. Oral mifepristone 600 mg and

vaginal gemeprost for midtrimester induction of abortion. An open multicenter study. Contraception 1997;56(6):361–66.

- Tang OS, Thong KJ, Baird DT. Second trimester medical abortion with mifepristone and gemeprost: a review of 956 cases. Contraception 2001;64(1):29–32.
- 39. Cameron IT, Michie AF, Baird DT. Prostaglandin-induced pregnancy termination: further studies using gemeprost (16,16 dimethyl-trans-delta 2-PGE1 methyl ester) vaginal pessaries in the early second trimester. Prostaglandins 1987;34(1): 111–17.
- 40. Thong KJ, Baird DT. An open study comparing two regimens of gemeprost for the termination of pregnancy in the second trimester. Acta Obstetricia et Gynecologica Scandinavica 1992;71(3):191–96.
- 41. Armatage RJ, Luckas MJ. A randomized trial of 2 regimens for the administration of vaginal prostaglandins (gemeprost) for the induction of midtrimester abortion. Australian and New Zealand Journal of Obstetrics and Gynaecology 1996;36(3):296–99.
- 42. Wong KS, Ngai CS, Wong AY, et al. Vaginal misoprostol compared with vaginal gemeprost in termination of second trimester pregnancy. A randomized trial. Contraception 1998;58(4):207–10.
- 43. Bebbington MW, Kent N, Lim K, et al. A randomized controlled trial comparing two protocols for the use of misoprostol in midtrimester pregnancy termination. American Journal of Obstetrics & Gynecology 2002;187(4):853–57.
- 44. Jain JK, Meckstroth KR, Mishell DR, Jr. Early pregnancy termination with intravaginally administered sodium chloride solution-moistened misoprostol tablets: historical comparison with mifepristone and oral misoprostol. American Journal

of Obstetrics & Gynecology 1999;181(6):1386-91.

- 45. Wong KS, Ngai CS, Yeo EL, et al. A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: a randomized comparative trial. Human Reproduction 2000;15(3):709–12.
- 46. Herabutya Y, Chanrachakul B, Punyavachira P. Vaginal misoprostol in termination of second trimester pregnancy. Journal of Obstetrics and Gynaecology Research 2000; 26(2):121–25.
- 47. Herabutya Y, Chanrachakul B, Punyavachira P. Second trimester pregnancy termination: a comparison of 600 and 800 micrograms of intravaginal misoprostol. Journal of Obstetrics and Gynaecology Research 2001; 27(3):125–28.
- Pongsatha S, Tongsong T. Second trimester pregnancy termination with 800 mcg vaginal misoprostol. Journal of Medical Association of Thailand 2001;84(6):859–63.
- 49. Dodd JM, Crowther CA. Misoprostol versus cervagem for the induction of labour to terminate pregnancy in the second and third trimester: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology 2006 Mar 1;125(1):3–8.
- 50. Ho PC, Blumenthal PD, Gemzell-Danielsson K, et al. Misoprostol for the termination of pregnancy with a live fetus at 13 to 26 weeks. International Journal of Gynecology & Obstetrics 2007;99(Suppl 2): S178–81.
- 51. Bartley J, Brown A, Elton R, et al. Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation. Human Reproduction 2001;16(10): 2098–102.
- 52. Van Look PF, Bygdeman M. Antiprogestational steroids: a

new dimension in human fertility regulation. Oxford Reviews of Reproductive Biology 1989;11:2–60.

- Thong KJ, Baird DT. Induction of second trimester abortion with mifepristone and gemeprost. British Journal of Obstetrics & Gynaecology 1993; 100(8):758–61.
- 54. Gemzell-Danielsson K, Ostlund E. Termination of second trimester pregnancy with mifepristone and gemeprost. The clinical experience of 197 consecutive cases. Acta Obstetricia et Gynecologica Scandinavica 2000;79(8):702–06.
- 55. Hamoda H, Ashok PW, Flett GM, et al. Analgesia requirements and predictors of analgesia use for women undergoing medical abortion up to 22 weeks of gestation. BJOG 2004;111(9): 996–1000.
- 56. Li CF, Wong CY, Chan CP, et al. A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. Contraception 2003;67(2):101–05.
- 57. Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. Contraception 1997;56(3):165–68.
- 58. Fiala C, Swahn ML, Stephansson O, et al. The effect of nonsteroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13–22 weeks gestation. Human Reproduction 2005; 20(11):3072–77.
- 59. Ashok PW, Templeton A, Wagaarachchi PT, et al. Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. Contraception 2004;69(1):51–58.
- 60. Norman JE. Uterine rupture during therapeutic abortion in the second trimester using mifepristone and prostaglandin. British Journal of

Obstetrics and Gynaecology 1995;102(4):332–33.

- Chen M, Shih JC, Chiu WT, et al. Separation of cesarean scar during second-trimester intravaginal misoprostol abortion. Obstetrics & Gynecology 1999;94(5 Pt 2):840.
- 62. Wiener JJ, Evans AS. Uterine rupture in midtrimester abortion. A complication of gemeprost vaginal pessaries and oxytocin. Case report. British Journal of Obstetrics and Gynaecology 1990;97(11):1061–62.
- 63. Atienza MF, Burkman RT, King TM. Midtrimester abortion induced by hyperosmolar urea and prostaglandin F2 alpha in patients with previous cesarean section: clinical course and potential for uterine rupture. American Journal of Obstetrics & Gynecology 1980;138(1):55–59.
- Royal College of Obstetricians and Gynaecologists. Termination of Pregnancy for Fetal Abnormality in England, Scotland and Wales. London: RCOG, 1996.
- 65. Drey EA, Foster DG, Jackson RA, et al. Risk factors associated with presenting for abortion in the second trimester. Obstetrics & Gynecology. 2006 Jan;107(1): 128–35.
- 66. Elimian A, Verma U, Tejani N. Effect of causing fetal cardiac asystole on second-trimester abortion. Obstetrics & Gynecology 1999;94(1):139–41.
- 67. Bhide A, Sairam S, Hollis B, et al. Comparison of feticide carried out by cordocentesis versus cardiac puncture. Ultrasound in Obstetrics and Gynecology 2002;20(3):230–32.
- Senat MV, Fischer C, Bernard JP, et al. The use of lidocaine for feticide in late termination of pregnancy. BJOG 2003;110(3): 296–300.
- 69. Ashok PW, Templeton A. Nonsurgical mid-trimester termination of pregnancy: a review of 500 consecutive cases. British Journal of Obstetrics

and Gynaecology 1999;106(7): 706–10.

- 70. Gautam R, Agrawal V. Early medical termination pregnancy with methotrexate and misoprostol in lower segment cesarean section cases. Journal of Obstetrics and Gynaecology Research 2003;29(4):251–56.
- Miller DA, Diaz FG, Paul RH. Vaginal birth after cesarean: a 10-year experience. Obstetrics & Gynecology 1994;84(2): 255–58.
- 72. Boulot P, Hoffet M, Bachelard B, et al. Late vaginal induced abortion after a previous cesarean birth: potential for

uterine rupture. Gynecologic and Obstetric Investigation. 1993;36(2):87–90.

73. Berghahn L, Christensen D, Droste S. Uterine rupture during second-trimester abortion associated with misoprostol. Obstetrics & Gynecology 2001; 98(5 Pt. 2):976–77.

Résumé

Les avortements du deuxième trimestre représentent de 10 à 15% des interruptions de grossesse dans le monde, mais ils sont responsables des deux tiers des plus graves complications liées à l'avortement. Ces dix dernières années, les méthodes médicamenteuses d'avortement du deuxième trimestre se sont sensiblement améliorées et sont devenues plus sûres et plus accessibles. Aujourd'hui, dans la plupart des cas, des services d'avortement médicamenteux sûrs et efficaces peuvent être proposés ou n'exigent que quelques changements dans les établissements sanitaires existants. L'avortement médicamenteux du deuxième trimestre peut être assuré par une infirmière-sagefemme, avec l'appui d'un gynécologue ; en raison du risque d'abondants saignements vaginaux et de graves complications, il est souhaitable qu'il se déroule dans un centre de santé pouvant pratiquer une transfusion sanguine ou une intervention chirurgicale d'urgence (y compris une laparotomie). Cet article donne des informations de base sur les schémas recommandés pour les avortements médicamenteux du deuxième trimestre. L'association de mifépristone et de misoprostol est maintenant une méthode confirmée et très efficace. Quand la mifépristone n'est pas disponible ou trop onéreuse, le misoprostol seul s'est aussi révélé efficace, même si la dose doit être augmentée et si l'efficacité est moindre. Par conséquent, chaque fois que possible, il convient d'utiliser l'association des deux médicaments. Il faut s'efforcer de réduire les évacuations chirurgicales inutiles de l'utérus après l'expulsion du fœtus. Les études futures devraient porter sur l'amélioration de la prise en charge de la douleur, le traitement des échecs de l'avortement médicamenteux dans les 24 heures et la sécurité des schémas d'avortement médicamenteux chez les femmes ayant subi une césarienne ou présentant une cicatrice utérine.

Resumen

Los abortos de segundo trimestre constituyen del 10 al 15% de todos los abortos inducidos mundialmente pero son responsables de dos terceras partes de las complicaciones más graves relacionadas con el aborto. Durante la última década, los métodos médicos para el aborto inducido en el segundo trimestre han mejorado considerablemente y son seguros y más accesibles. Hoy, en la mayoría de los casos, es posible ofrecer o mejorar servicios seguros y eficientes de aborto con medicamentos haciendo pequeños cambios a los establecimientos de salud. El aborto con medicamentos puede ser efectuado en el segundo trimestre por una enfermera-partera profesional con el respaldo de un ginecólogo. Dado el potencial de hemorragia vaginal y graves complicaciones, se aconseja que el aborto de segundo trimestre se efectúe en una unidad donde sea posible realizar una transfusión sanguínea o cirugía de urgencia (incluida la laparotomía). En este artículo se proporciona información básica sobre los regímenes recomendados para el aborto con medicamentos en el segundo trimestre. La combinación de mifepristona y misoprostol ahora es un método establecido y muy eficaz para el aborto de segundo trimestre. En los lugares donde no se dispone de mifepristona o donde no es asequible, se ha mostrado que misoprostol solo también es eficaz, aunque se necesita una dosis total más alta y su eficacia es menor que la del régimen combinado. Por tanto, siempre que sea posible, se debe utilizar el régimen combinado. Se deben realizar esfuerzos por reducir el número de procedimientos innecesarios de evacuación endouterina quirúrgica después de la expulsión del feto. Futuros estudios deberían centrarse en mejorar el manejo del dolor, el tratamiento de mujeres cuyo aborto con medicamentos fracase después de 24 horas y la seguridad de los regímenes de aborto con medicamentos en mujeres con antecedentes de cesáreas o cicatrices uterinas.