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Clinical Updates in Reproductive Health

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Clinical Updates in Reproductive Health

July 2013

Clinical Updates in Reproductive Health are designed to provide Ipas staff, trainers, partners and other health-care providers with access to up-to-date, evidence-based recommendations. In general, the recommendations are the same as those in the World Health Organization's 2012 *Safe Abortion: Technical and Policy Guidance for Health Systems, Second edition*. In rare cases, the recommendations have been modified due to the settings where we work. In addition, if there is more current evidence to inform the recommendations, they will be updated here.

Ipas works around the world to increase women's ability to exercise their sexual and reproductive rights, especially the right to safe abortion. You can find more information at www.ipas.org.

Revisions: This document is updated twice a year; please see the “last reviewed” date for each topic. The information for each *Clinical Update* topic is current through the listed “last reviewed” date, meaning all relevant published literature up to that date has been considered and included where appropriate.



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Ipas works globally to increase women's ability to exercise their sexual and reproductive rights and to reduce abortion-related deaths and injuries. We seek to expand the availability, quality and sustainability of abortion and related reproductive health services, as well as to improve the enabling environment. Ipas believes that no woman should have to risk her life or her health because she lacks safe reproductive health choices.

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Making Ipas clinical recommendations

When a specific clinical recommendation is made within Ipas's *Clinical Updates in Reproductive Health*, there are two elements included to help put the clinical information in perspective:

1. Quality of evidence
2. Strength of the recommendation

Quality of evidence reflects the extent to which we can be *confident* that an *estimate of the effect of an intervention* is adequate to support recommendations (Guyatt et al., 2008).

Strength of a recommendation reflects the extent to which we can be *confident* that the desirable effects of an intervention outweigh the undesirable effects (Guyatt, Oxman, Kunz, Falck-Ytter et al. 2008). In other words, adherence to the recommendation will *do more good than harm*.

Last reviewed: May 21, 2013

Quality of evidence

Clinical evidence, and the recommendations based on the evidence, can be of varying quality. Sources of evidence range from small studies or case reports to well-designed large clinical studies that have minimized bias. The quality of evidence is defined as the "extent to which one can be confident that an estimate of effect or association is correct."

When assessing the quality of evidence, the following criteria are considered (Oxman & Group, 2004):

1. the study design
2. the consistency of the results across available studies
3. precision of the results (wide or narrow confidence intervals)
4. the applicability with respect to populations, interventions and settings where the proposed intervention may be used
5. the likelihood of publication bias

Ipas uses the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, a four-level system of grading quality of evidence that works as follows:

- A **high** grade is assigned when further research is very unlikely to change our confidence in the estimate of effect.
- A **moderate** grade indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- A **low** grade indicates that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- A **very low** grade is reserved for when any estimate of effect is very uncertain.

Based on these grading criteria, randomized trials are initially given a high grade, observational studies are initially labeled as having a low quality of evidence, and any other evidence is very low. However, the grade could

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decrease if the evidence is based on poor study quality, inconsistent results, indirect evidence, imprecise or sparse data, or a high probability of reporting bias. The grade could increase if there is a strong association between the intervention and the outcome.

Strength of a recommendation

Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies (for example, manual vacuum aspiration versus dilatation and curettage), quality of evidence, variability in clients' values and preferences, and resource availability and use (Guyatt, Oxman, Kunz, Falck-Ytter et al. 2008). Desirable effects can include improved health outcomes, less burden for providers and health systems, and greater savings. Undesirable effects can include harm to patients, greater burden (for example, the demands of adhering to an onerous recommendation) and increased costs.

Strong recommendations are granted when the desirable effects of an intervention or adherence with a recommendation clearly outweigh the undesirable effects (Guyatt, Oxman, Vist et al. 2008).

Weak recommendations are made when evidence suggests that desirable effects of an intervention and recommendation probably outweigh the undesirable effects but there are small benefits or benefits that may not be worth the costs, and there is an absence of high-quality evidence (Guyatt, Oxman, Vist et al. 2008).

The difficulty in developing guidelines based on quality of evidence is that the studies evaluated may not have comparable patient populations, health-care settings or resources as those to whom the recommendations are targeted. Those developing guidelines should take into account the patient population, nature of the intervention, cost-effectiveness and opportunity cost of an alternate intervention, feasibility of intervention in the specified health-care setting, and societal cost (Guyatt, Oxman, Vist et al. 2008; Guyatt, Oxman, Kunz, Jaeschke et al. 2008; WHO 2012). Similar to the World Health Organization's approach, Ipas should help countries "localize" recommendations by providing technical assistance when necessary.

Can you have a strong recommendation based on low-quality evidence?

Yes. There are many factors that influence the strength of a recommendation.

For example, although there is limited evidence about the safety and efficacy of providing hormonal contraception during medical abortion, several factors increase the strength of the recommendation that women can be offered hormonal contraception at the time of the first pill of a medical abortion regimen: 1) the value of integrating contraception into abortion care to prevent unintended pregnancy, 2) the low theoretical risk that it interferes with the mechanism of action of mifepristone or misoprostol, and 3) the risk that women who do not get a contraceptive method at the time of abortion will not return.

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First-trimester vacuum aspiration and medical abortion: Screening for ectopic pregnancy

Recommendation:

Ectopic pregnancy should be considered in women presenting for abortion who also have a concerning history or exam.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 22, 2013

Background

Although the rate of ectopic pregnancy in women seeking abortion is less than one percent (Edwards & Creinin, 1997), ectopic pregnancy is a leading cause of maternal mortality in the first trimester (CDC, 1995; Khan, Wojdyla, Say, Gulmezoglu, & Van Look, 2006; WHO, 1985).

Risk factors

A woman's medical history and physical exam may indicate an increased risk of ectopic pregnancy; however, half of all ectopic pregnancies occur in women with no risk factors and a benign clinical presentation (Stovall, Kellerman, Ling, & Buster, 1990). Risk factors with the highest associated risk of ectopic pregnancy in pregnant women are shown in this table:

Risk factor	Risk of ectopic in the current pregnancy
Previous ectopic pregnancy	10-15 percent (Yao & Tulandi, 1997)
History of tubal surgery, including sterilization	25-50 percent (Barnhart, 2009)
IUD in place	25-50 percent (Barnhart, 2009)

Other risk factors—such as a history of infertility and assisted reproductive technology, a history of genital or pelvic infections, multiple partners, early age at first intercourse, and smoking—confer lower risks (Barnhart, 2009).

Screening

Providers should screen women for risk factors for ectopic pregnancy during the history and physical exam. A screening checklist should include relevant history, such as a history of ectopic pregnancy, tubal ligation, tubal surgery or an IUD in place. The screening checklist should also include signs and symptoms, such as an adnexal mass or pain on examination, or pain and vaginal bleeding.

Treatment for high-risk women

A woman desiring abortion who has risk factors for ectopic pregnancy with a benign physical exam can be evaluated further with ultrasound or serial hCG testing, but access to testing may be limited in low-resource settings (Obed, 2006). A provider may also offer a woman vacuum aspiration with tissue examination to confirm

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the diagnosis of intrauterine pregnancy rather than a medical abortion. A woman with suspicious signs and symptoms or a concerning physical exam should be diagnosed and treated as soon as possible or transferred immediately to a facility that can manage ectopic pregnancy. Early diagnosis and treatment of ectopic pregnancy can help preserve fertility and save women's lives.

Post-procedure screening

For women undergoing vacuum aspiration, the products of conception should be strained and examined to confirm products of conception in the aspirate. If products of conception are not seen, ectopic pregnancy should be suspected and followed closely.

Young women

The recommendation for screening for ectopic pregnancy is the same for young women as it is for adult women.

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First-trimester vacuum aspiration: Safety of vacuum aspiration for adolescent and young women

Recommendation:

- Vacuum aspiration for adolescent and young women is very safe and should be offered as a method of safe abortion.
- Cervical preparation may be considered for young adolescents prior to vacuum aspiration due to their increased risk of cervical injury.
- Clinical services should promote timely access to safe abortion for young women.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: June 18, 2013

Background

The World Health Organization defines adolescents as individuals between 10 and 19 years of age, and young women as between 20 and 24 years of age. Adolescents face barriers to accessing safe abortion care and present for abortions at later gestational ages than adult women (Pazol, Creanga, Zane, Burley, & Jamieson, 2012). Adolescents are at increased risk of complications of unsafe abortion due to delays seeking care, seeking care from unskilled providers and not accessing services when complications arise (Olukoya, Kaya, Ferguson, & AbouZahr, 2001). Increasing access to safe abortion is beneficial for young women.

Safety of vacuum aspiration

A large prospective United States multi-center cohort study of 164,000 women undergoing legal abortion, 50,000 of whom were adolescents, found that mortality and major morbidity were lower in adolescents (Cates Jr, Schulz, & Grimes, 1983). The mortality rate was 1.3 per 100,000 in women under 20 years old compared to 2.2 per 100,000 in women age 20 and older. Serious adverse events including major surgery, hemorrhage with transfusion, and uterine perforation were less common in women under age 20.

Cervical injury

In large prospective cohort studies, very young age (<17 years old) has been associated with cervical injury during vacuum aspiration even after controlling for nulliparity (Cates Jr, et al., 1983; Schulz, Grimes, & Cates, 1983). Cervical preparation may be considered for young women prior to first-trimester vacuum aspiration (Allen & Goldberg, 2007; WHO, 2012).

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First-trimester vacuum aspiration: Cervical preparation

Recommendation:

Cervical preparation is recommended after 12 to 14 weeks. Before 12 to 14 weeks, cervical preparation may be offered but does not need to be routinely used (WHO, 2012).

Recommended methods for cervical preparation in the first trimester include:

- Misoprostol 400mcg sublingually two to three hours before the procedure
- Misoprostol 400mcg vaginally three hours before the procedure
- Mifepristone 200mg orally 24 to 48 hours before the procedure
- Osmotic dilators placed in the cervix 6 to 24 hours before the procedure

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 22, 2013

Background

Cervical preparation is recommended before surgical abortion for all women over 12 to 14 weeks gestation to prevent complications (Fox & Hayes, 2007; Kapp, Lohr, Ngo, & Hayes, 2010; WHO, 2012). For women at higher risk of complications (young women, nulliparous women, women with cervical abnormalities, or women at later gestational ages) or inexperienced providers there may be a benefit from cervical preparation even before 12 to 14 weeks gestation (Allen & Goldberg, 2007; Grimes, Schulz, & Cates, 1984; Kaunitz, Rovira, Grimes, & Schulz, 1985).

Benefits of cervical preparation

A meta-analysis of 51 randomized controlled clinical trials of cervical preparation in the first trimester showed that procedure time was shorter with cervical preparation but there was no difference in serious outcomes like cervical laceration or uterine perforation in women who were given cervical preparation compared to placebo (Kapp, et al., 2010). The largest multicenter randomized controlled trial of 2,485 women given misoprostol 400mcg vaginally or placebo three hours before a vacuum aspiration showed no difference in the rates of cervical laceration, perforation or infection between the two groups. In this study, the risk of incomplete abortion was lower in the misoprostol group (<1 percent) compared to the placebo group (2 percent), but side-effects were more frequent for women who took misoprostol (Meirik, Huong, Piaggio, Bergel, & von Hertzen, 2012).

Side-effects of cervical preparation

In randomized controlled trials, side-effects of cervical preparation are common (Kapp & vonHertzen, 2009; Meirik, et al., 2012). In the largest randomized controlled trial of misoprostol, 55 percent of women who took misoprostol complained of abdominal pain and 37 percent had vaginal bleeding compared to 22 percent and seven percent in the placebo group (Meirik, et al., 2012). In addition, cervical preparation adds cost, complexity and time to an abortion as women must visit the clinic a day before the procedure to get osmotic dilators or mifepristone or wait in the clinic for two to three hours for misoprostol to work. Because first-trimester abortion is so safe, the gestational age at which the benefit of cervical preparation outweighs the side-effects is not known

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(Kapp, et al., 2010). Women's satisfaction with cervical preparation has not been studied in randomized controlled trials (Kapp, et al., 2010) but is an important consideration for quality of care and service delivery.

Choice of methods

If cervical preparation is used, the choice of vaginal or sublingual misoprostol, oral mifepristone or osmotic dilators may be based on availability, expense, convenience and preference. Sublingual misoprostol has superior efficacy but more gastrointestinal side effects than vaginal misoprostol (Kapp, et al., 2010). Mifepristone given 24 hours prior to the abortion is superior to misoprostol but adds time and expense to the abortion procedure (Ashok, Flett, & Templeton, 2000). Misoprostol and laminaria have similar efficacy but laminaria placement has increased pain, increased time to procedure and reduced satisfaction for women (Burnett, Corbett, & Gertenstein, 2005; MacIsaac, Grossman, Balistreri, & Darney, 1999).

Young women

Young women may benefit from cervical preparation due to their increased risk of cervical injury during abortion (Schulz, Grimes, & Cates, 1983), but there are no clinical trial data to support the use of cervical preparation in this patient population.

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First-trimester vacuum aspiration: Paracervical anesthesia

Recommendation:

- Paracervical anesthesia is recommended as a component of pain management during first-trimester vacuum aspiration procedures.
- Mid-level providers may give paracervical anesthesia during first-trimester aspiration procedures.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 22, 2013

Evidence

Many providers use local anesthesia or paracervical block (PCB) for pain management during first-trimester vacuum aspiration (O'Connell et al., 2009). In a recent randomized controlled trial of 120 women undergoing first-trimester aspiration abortion, women who received PCB had less pain during dilation and aspiration compared to women who received a sham injection. In this study, the overall rate of complications was low and there was no difference between the two groups (Renner, 2012).

Technique (Renner, 2012)

- Load a 20mL syringe with 18mL of lidocaine (one percent) buffered with 2mL sodium bicarbonate (8.4 percent).
- Attach syringe to a 20-gauge spinal needle.
- Infiltrate 2mL into the cervix superficially at the tenaculum site (located at 12 o'clock).
- Grasp the cervix with the single-tooth tenaculum.
- Inject the remaining 18mL in equal amounts at the cervicovaginal junction at the locations of two, four, eight and 10 o'clock. The injection should be continuous from superficial to a depth of three centimeters.
- Pull back on the plunger before injecting anesthesia to prevent intravascular injection.
- Begin dilation three minutes after the PCB is complete.

Mid-level providers

In an international randomized multicenter study comparing physician and mid-level providers, mid-level provider had similar safety and efficacy rates as physicians when performing first-trimester vacuum aspiration with paracervical block (Warriner et al., 2006).

Young women

This recommendation is the same for young women as for adult women.

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First-trimester vacuum aspiration: Pain management

Recommendation:

- Women undergoing first-trimester vacuum aspiration should receive pain medications and non-pharmacologic approaches to treat pain (WHO, 2012).
- General anesthesia is not routinely recommended for first-trimester pain management.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: May 29, 2013

Background

Most women undergoing first-trimester vacuum aspiration will experience pain (Smith, Stubblefield, Chirchirillo, & McCarthy, 1979). Clinicians consistently underestimate the amount of pain women experience during abortion (Singh et al., 2008).

Methods of pain management

For first-trimester vacuum aspiration, a combination of pain medications, local anesthesia (in the form of a paracervical block), and non-pharmacologic measures typically provide pain relief for most women (WHO 2012). Intravenous sedation may also be offered. General anesthesia increases the risks associated with abortion and is not recommended for routine procedures (Atrash, Cheek, & Hogue, 1988).

Pain medication

Premedication with non-steroidal anti-inflammatory drugs has been shown in clinical trials to decrease pain during and after the procedure (Roche, Li, James, Fechner & Tilak, 2012; Romero, Turok, & Gilliam, 2008; Suprpto & Reed, 1984; Wiebe & Rawling, 1995). Premedication with narcotic analgesics also provides pain relief but may be less effective than non-steroidal anti-inflammatory drugs (Khazin et al., 2011; Lowenstein et al., 2006; Romero, Turok & Gilliam, 2008). A randomized controlled trial of hydrocodone-acetaminophen compared to placebo showed that the addition of hydrocodone-acetaminophen to standard premedication with ibuprofen did not improve pain management and increased postoperative nausea (Micks et al., 2012). Anxiolytics such as lorazepam may be of benefit to some women, but clinical trial evidence does not support their routine use (Wiebe, Podhradsky & Dijak, 2003). Paracetamol is not effective for pain relief during vacuum aspiration (Cade & Ashley, 1993).

Local anesthesia

A paracervical block with 20mL of lidocaine (one percent) given three minutes before dilating the cervix has been shown to decrease pain with dilation and aspiration (Renner, Nichols, Jensen, Li, & Edelman, 2012). Paracervical block is a low risk procedure that can be performed by physicians and mid-level providers (Warriner et al., 2006).

Non-pharmacologic pain management

Medications should be supplemented with supportive techniques to decrease pain and anxiety. Some techniques that may be helpful include respectful staff, a clean and private setting, counseling, verbal support, gentle surgical

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technique, listening to music during the procedure and a heating pad or hot water bottle in the recovery room.

Intravenous sedation

Intravenous sedation using a combination of narcotics and anxiolytics is an effective means of pain control and improves satisfaction with the abortion procedure (Allen, Kumar, Fitzmaurice, Lifford & Goldberg, 2006; Wong, Ng, Ngai & Ho, 2002). However, providing intravenous sedation increases the expense, complexity and potential risks of an abortion procedure. The increased monitoring necessary to deliver intravenous sedation safely requires facility investments in training and equipment.

Young women

Young and nulliparous women report increased pain during abortion procedures (Belanger, Melzack & Lauzon, 1989; Smith et al., 1979). Being attentive to young women's needs for pain management increases the quality of abortion care.

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First-trimester vacuum aspiration: Prophylactic antibiotics

Recommendation:

Administer prophylactic antibiotics for all women prior to vacuum aspiration (WHO, 2012). Where antibiotics are unavailable, uterine aspiration may still be offered. Therapeutic antibiotics should be administered to all women who are suspected of or who have been diagnosed with an infection.

Strength of recommendation: Strong

Quality of evidence: High

Last reviewed: May 22, 2013

Background

A Cochrane meta-analysis of 19 randomized controlled clinical trials showed that administration of prophylactic antibiotics at the time of vacuum aspiration in the first trimester significantly reduces the risk of postabortal infection (Low, Mueller, Van Vliet, & Kapp, 2012). The World Health Organization (WHO, 2012), Society of Family Planning (Achilles & Reeves, 2011) American Congress of Obstetricians and Gynecologists (ACOG, 2009) and Royal College of Obstetricians and Gynaecologists (RCOG, 2011) recommend prophylactic antibiotics for all women having a vacuum aspiration. Giving prophylactic antibiotics is more effective (Levallois & Rioux, 1988) and cheaper (Penney et al., 1998) than screening all women and treating only those with evidence of infection. The inability to provide antibiotics should not limit access to abortion (WHO, 2012), as the overall risk of infection with vacuum aspiration is very low.

Regimen

Many antibiotic regimens for abortion prophylaxis have been studied, but the ideal antibiotic, dose and timing has not yet been established (Achilles & Reeves, 2011; Low, Mueller, Van Vliet, & Kapp, 2012). Tetracyclines (doxycycline) and nitroimidazoles (metronidazole and tinidazole) are commonly used because of their clinical efficacy, oral availability, low cost and low risk of allergic reactions (Achilles & Reeves, 2011). Although studies of abortion are limited, (Caruso et al., 2008) evidence from the obstetrical (Costantine et al., 2008), gynecologic (Mittendorf et al., 1993) and general surgery (Classen et al., 1992) literature supports the practice of giving antibiotics before the procedure to decrease the risk of infection. To reduce the incidence of nausea with pre-operative antibiotics, doxycycline may be given up to 10-12 hours before the procedure with a meal (Darj, Stralin, & Nilsson, 1987). Antibiotic regimens do not need to be extended beyond the immediate postabortion period (Achilles & Reeves, 2011; Levallois & Rioux, 1988; Caruso et al., 2008; Lichtenberg & Shott, 2003).

The following table lists some common regimens used in clinical practice or recommended by professional organizations. These regimens are based on clinical evidence and expert opinion. Providers should choose a regimen based on the expense and availability of the antibiotics as well as practices around testing and treating women for sexually transmitted infections.

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Common Regimens	Recommender
<p>Doxycycline 100mg orally one hour before the procedure and 200mg after the procedure</p> <p><i>or</i></p> <p>Metronidazole 500mg orally twice daily for five days</p>	American College of Obstetricians and Gynecologists (ACOG, 2009)
<p>Azithromycin 1g orally on the day of abortion plus metronidazole 1g rectally or 800mg orally prior to or at the time of abortion</p> <p><i>or</i></p> <p>Doxycycline 100mg orally twice daily for seven days starting on the day of abortion, plus metronidazole 1g rectally or 800mg orally prior to or at the time of abortion</p> <p><i>or</i></p> <p>Metronidazole 1g rectally or 800mg orally prior to or at the time of abortion for women who have tested negative for <i>C. trachomatis</i> infection</p>	Royal College of Obstetricians and Gynaecologists (RCOG, 2011)
<p>Doxycycline 100mg orally twice daily for three days starting on the day of the abortion</p>	Planned Parenthood Federation of America (PPFA, 2011)

Therapeutic antibiotics

If possible, women at high risk should be screened and treated for sexually transmitted infections in addition to receiving prophylactic antibiotics. Women who have signs and symptoms of active infection should be provided with abortion services without delay and treated appropriately once the procedure is completed.

Young women

This recommendation is the same for young women as for adult women.

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First-trimester vacuum aspiration: Postabortion contraception

Recommendation:

- Immediate initiation of hormonal and non-hormonal contraception and sterilization following first-trimester aspiration abortion is encouraged and considered safe.
- Intrauterine devices (IUD) placement or female sterilization can be performed immediately following a successful, uncomplicated abortion.
- Long-acting contraceptive methods have higher continuation rates and lower repeat pregnancy rates compared to short-acting methods.

Strength of recommendation: Strong

Quality of evidence:

- IUDs and combined oral contraceptives (COCs): High
- Other methods: Low to Moderate

Last reviewed: May 29, 2013

Fertility return

A woman may ovulate within 10 days of an abortion (Boyd et al., 1972) and can become pregnant if she resumes sexual intercourse without using a modern contraceptive method (Wolf et al., 1994).

Safety and acceptability of postabortion contraception

The 2009 WHO *Medical Eligibility Criteria for Contraceptive Use* classifies all contraceptive methods as category one, or safe for immediate use, following first-trimester uncomplicated aspiration abortion. Sterilization is classified as acceptable after an uncomplicated abortion. Male sterilization may be performed at any time. Fertility awareness-based methods may be initiated once a woman has had at least one postabortion menses.

In comparison to short-acting methods such as oral contraceptive pills, long-acting methods of birth control such as implants and IUDs have higher continuation rates and lower repeat pregnancy rates than other methods (Blumenthal, Wilson, Remsburg, Cullins & Huggins, 1994; Cameron et al., 2012; Peipert, Madden, Allsworth & Secura, 2012; Roberts, Silva & Xu, 2010).

Evidence related to specific contraceptive methods

Combined oral contraceptives (COCs):

A recent review of seven studies including 1,739 women demonstrated no serious adverse events using COCs immediately after abortion (Gaffield, Kapp & Ravi, 2009). Additionally, women who used COCs immediately demonstrate similar bleeding patterns to women using no contraception, and less bleeding than copper IUD users.

Combined vaginal ring:



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A cohort study of 81 women who placed a vaginal ring one week after abortion showed no serious adverse events or infections (Fine, Tryggstad, Meyers & Sangi-Haghpeykar, 2007).

Progestin-only injection:

A study of 132 women using depot medroxyprogesterone acetate immediately after abortion reported no serious adverse events but low method continuation rates (22 percent) at one year and high repeat pregnancy rates (Goldberg, Cardenas, Hubbard & Darney, 2002).

Progestin-only subdermal implants:

Cohorts of women using the etonogestrel contraceptive implant immediately after abortion show high continuation rates, similar to those of women with interval placement (Madden et al., 2012; Mark, Borgatta & Sonalkar 2013).

Intrauterine devices (IUDs):

A 2010 Cochrane review of eleven randomized trials with 7,405 women concluded that IUD insertion immediately after abortion is safe and practical (Grimes, Lopez, Schulz & Stanwood, 2010). This review found no differences in serious adverse events, such as infection or perforation, between immediate and delayed placement. Expulsion rates were slightly higher with immediate insertion but so were long-term continuation rates. In a recent randomized controlled trial that assigned 575 women to either immediate or delayed insertion, those with delayed insertion were less likely to obtain the device and more likely to have a repeat pregnancy (Bednarek et al., 2011). Requiring a follow-up visit for IUD insertion is a significant barrier to obtaining the IUD (Stanek, Bednarek, Nichols, Jensen & Edelman, 2009).

Young women

The IUD for women under the age of 20 is classified by WHO as category two, in which the benefits generally outweigh the risks. While risk is slightly increased due to higher rates of sexually transmitted infections and expulsion in this patient population, IUDs are still a safe, effective and recommended method for women under the age of 20. Sterilization may be performed, but a young woman will need special precautions due to the increased risk of regret (WHO, 2009).

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First-trimester medical abortion: Safety and efficacy of medical abortion for adolescent and young women

Recommendation:

- Medical abortion for adolescent and young women is safe, effective and acceptable and should be offered as a method of safe abortion to this population.
- Clinical services should promote timely access to safe abortion for young women.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: June 18, 2013

Background

The World Health Organization defines adolescents as individuals between 10 and 19 years of age, and young women as between 20 and 24 years of age. Adolescents face barriers to accessing safe abortion care and present for abortions at later gestational ages than adult women (Pazol, Creanga, Zane, Burley, & Jamieson, 2012). Adolescents are at increased risk of complications of unsafe abortion due to delays seeking care, seeking care from unskilled providers and not accessing services when complications arise (Olukoya, Kaya, Ferguson, & AbouZahr, 2001). Increasing access to safe abortion, including medical abortion, is beneficial for young women.

Efficacy of medical abortion

Clinical trials and cohort studies have shown young women have the same (Haimov-Kochman et al., 2007; Heikinheimo, Leminen, & Suhonen, 2007) or increased (Niinimäki et al., 2011; Shannon et al., 2006) success rates when using mifepristone and misoprostol for medical abortion compared to older women. A large Finnish population-based retrospective cohort study that compared 3,024 adolescents to 24,006 adult women up to 20 weeks gestational age showed that the risk of needing surgical evacuation following medical abortion was significantly lower in adolescents (adjusted odds ratio [OR] = 0.78, 95% confidence interval [CI] = 0.67 to 0.90) compared to adult women (Niinimäki, et al., 2011). In a prospective cohort that included young women, the efficacy of misoprostol-only medical abortion was the same for young women and older women (Bugalho et al., 1996).

Safety of medical abortion

Despite higher rates of chlamydia infection, in a large population-based retrospective cohort study of women up to 20 weeks gestational age, complication rates were similar or lower among adolescents than among adult women, even when controlling for nulliparity. In this study, adolescents had a significantly lower incidence of hemorrhage (OR = 0.87, 95% CI = 0.77 to 0.99), incomplete abortion (OR = 0.69, 95% CI = 0.59 to 0.82), and need for surgical evacuation (OR = 0.78, 95% CI = 0.67 to 0.90). Postabortion infection occurred at similar rates in both cohorts (OR = 0.97, 95% CI = 0.73 to

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1.30)(Niinimäki, et al., 2011).

Acceptability of medical abortion

In one small, non-comparative study of 28 adolescents age 14 to 17 using mifepristone and misoprostol medical abortion, 96 percent of adolescents found medical abortion acceptable and 79 percent reported satisfaction with the procedure by four weeks of follow-up (Phelps, Schaff, & Fielding, 2001).

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First-trimester medical abortion with mifepristone and misoprostol and misoprostol only: Estimating gestational age before medical abortion

Recommendation:

Gestational age can be calculated using a woman's report of her last menstrual period (LMP) combined with a clinician's bimanual exam. Use of routine ultrasound for gestational age determination is not necessary (WHO, 2012).

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 30, 2013

Background

Providers should determine gestational age to assess a woman's eligibility for medical abortion. Women and providers can accurately assess gestational age without routine ultrasound (Kaneshiro, Edelman, Sneeringer, & Ponce de Leon, 2011). If gestational age is misestimated, the result is usually not clinically significant because any reduction in effectiveness of medical abortion regimens as gestational age advances is gradual, not sudden (Hamoda, Ashok, Flett, & Templeton, 2005).

Last menstrual period

Most women can recall their last menstrual period (LMP) reasonably well regardless of their education and whether they usually record their LMP dates (Harper, Ellertson & Winikoff, 2002; Wegienka & Baird, 2005). In two multi-site international cohort studies of 1,221 women having medical abortion in China, Cuba, India and the United States, women were able to estimate their eligibility accurately over 90 percent of the time (Ellertson et al., 2000; Ellertson, Elul & Winikoff, 1997).

Bimanual examination

According to cohort studies of medical abortion, adding a bimanual exam to a woman's report of her LMP can help a clinician accurately determine gestational age (Blanchard et al., 2007; Bracken et al., 2011; W. Clark et al., 2010; W. H. Clark, Gold, Grossman & Winikoff, 2007; Fielding, Schaff & Nam, 2002). A cross-sectional multi-site study of 673 women in South Africa found that providers' estimates of gestational age were, on average, two days lower than ultrasound estimate and women's LMP estimates of gestational age were one day lower. The authors concluded that a combination of assessment of menstrual history and physical examination was sufficiently accurate to determine eligibility for medical abortion in most cases when compared to ultrasound (Blanchard, et al., 2007).

In a prospective study of 1,016 women at 15 sites in the United States, clinicians correctly estimated eligibility in 87 percent of women. In only one percent of cases did clinicians underestimate gestational age, a potentially important error in medical abortion if underestimation is clinically significant (Fielding, et al., 2002). Finally, a prospective trial of 4,484 women in 10 clinics in the United States showed that if women had gestational age

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estimated by LMP and a clinician exam, only 1.6 percent of them would have been inappropriately given medical abortion above the gestational age limit compared to when ultrasound was used (Bracken, et al., 2011).

Ultrasound

Ultrasound does not yield exact gestational age measurements due to variability in the sonographer, machines and software (Callen, 2000). In addition, an ultrasound has an inherent margin of error of three to five days before 12 weeks gestation, and the margin of error increases as the pregnancy advances (Hadlock, Shah, Kanon & Lindsey, 1992). For these reasons, if the LMP and ultrasound differ within five days in the first trimester, the LMP is usually used for dating. In cohort studies of medical abortion in low-resource settings such as India, Nepal, Vietnam and Tunisia, lack of ultrasound has not had an impact on the success of medical abortion (Coyaji et al., 2001; Elul et al., 2001; Warriner et al., 2011).

If a provider is unable to assess gestational age through the combination of LMP, history and bimanual examination, a more experienced clinician should perform a bimanual examination or the woman should be referred for an ultrasound. Any woman with a suspected ectopic pregnancy needs further evaluation.

Young women

This recommendation is the same for young women as for adult women.

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First-trimester medical abortion with mifepristone and misoprostol or misoprostol only: Pain management

Recommendation:

- All women undergoing medical abortion in the first trimester should be offered pain management (WHO, 2012).
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or diclofenac are more effective than paracetamol or acetaminophen.
- Narcotic analgesics and non-pharmacologic measures may also be used.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: May 29, 2013

Medications for pain management

In a study of 6,755 women using medical abortion in the first trimester, 78.4 percent reported moderate or severe pain and cramping when using the regimen (Goldstone, Michelson & Williamson, 2012). Multiple pain regimens have been studied in the literature with varying degrees of effectiveness (Jackson & Kapp, 2011). A randomized controlled trial of 120 women showed that ibuprofen is more effective than acetaminophen for pain during first-trimester medical abortion with mifepristone and misoprostol (Livshits et al., 2009). Ibuprofen can be given with misoprostol (Avraham et al., 2012) or once cramping starts (Livshits et al., 2009). Ibuprofen does not reduce the effectiveness of medical abortion.

Narcotic analgesics are another option for pain control, although the optimal drug, dose and timing are not known. One potential strategy is to provide women with nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotic analgesics and advise them to begin with NSAIDs either with misoprostol or once cramping starts and alternate the two medications if they continue to experience pain.

Non-pharmacologic pain management

In addition to medications, other methods that may help women manage pain during a medical abortion are thorough counseling, a supportive environment and applying a heating pad or hot water bottle to the lower abdomen. Music and guided imagery are effective for pain management during surgical abortion and may be helpful for medical abortion as well (Renner, Jensen, Nichols, & Edelman, 2009). These methods are complementary to but not adequate substitutes for pain management with medications.

Quality of evidence

There is limited trial data to establish the best regimen for pain control (Jackson & Kapp, 2011). The trials that exist use multiple regimens and are difficult to compare.

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Young women and nulliparous women have been shown to have higher analgesic requirements during medical abortion (Westhoff, Dasmahapatra, Winikoff & Clarke, 2000; Westhoff, Dasmahapatra & Schaff, 2000). Discussing pain control with young women and giving them the appropriate medications and instructions may be particularly important.

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First-trimester medical abortion with mifepristone and misoprostol or misoprostol only: Prophylactic antibiotics

Recommendation:

Routine use of antibiotics is not recommended for women undergoing medical abortion (WHO, 2012). Women who have signs or symptoms of sexually transmitted infection at the time of medical abortion should be treated appropriately and medical abortion can be provided without delay.

Strength of recommendation: Weak

Quality of evidence: Very low

Last reviewed: May 30, 2013

Risk of infection

The overall risk of infection found in prospective studies of medical abortion using mifepristone and a prostaglandin in the first trimester is approximately 0.3 percent (Achilles & Reeves, 2011). Serious infections requiring hospitalization are very uncommon, with rates in large US retrospective studies ranging from 0.03 percent to 0.09 percent (Fjerstad et al., 2009; Henderson, Hwang, Harper, & Stewart, 2005).

Infectious mortality

Nine cases of fatal clostridia sepsis occurred in North America following mifepristone and misoprostol medical abortion (Cohen et al., 2007; Fischer et al., 2005; Meites, Zane & Gould, 2010; Sinave, Le Templier, Blouin, Leveille & Deland, 2002). One death from group A *streptococcus* has been reported in Australia and one death from *Clostridium sordelli* has been reported in Portugal (Reis et al., 2011) in women who used mifepristone and misoprostol. Although the deaths are concerning, the overall infectious mortality rate related to medical abortion remains very low at 0.58 per 100,000 procedures (Meites et al., 2010). This rate is similar to the mortality rate after spontaneous abortion (Creinin, Blumenthal & Shulman, 2006).

Prophylactic antibiotics

There have been no randomized controlled trials examining the effect of antibiotic prophylaxis on medical abortion outcomes (Low, Mueller, Van Vliet & Kapp, 2012). A retrospective cohort study with historical controls from Planned Parenthood Federation of America showed that changing the route of administration of misoprostol from vaginal to buccal reduced the rate of serious infection from 0.093 percent to 0.025 percent, and routinely giving doxycycline twice a day for seven days starting on the day of mifepristone further reduced the rate to 0.006 percent (Fjerstad, et al., 2009). However, because the baseline rate of infection was so low, the number of women who had to take doxycycline to prevent a single serious infection was 5,000. Given the large number of women who would need to take antibiotics to prevent a single infection coupled with the expense and side effects of antibiotics, the American College of Obstetricians and Gynecologists (ACOG, 2009) the Society of Family Planning (Achilles & Reeves, 2011) and the World Health Organization (WHO, 2012) do not recommend routine antibiotic use. In contrast, the Royal College of Obstetricians and Gynaecologists recommends routine antibiotic use with medical abortion procedures (RCOG, 2011).

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First-trimester medical abortion with mifepristone and misoprostol or misoprostol only: Contraception

Recommendation:

- Hormonal methods including pills, patches, rings, injections or implants may be started on the day of the first pill of medical abortion (WHO, 2012).
- IUD insertion and sterilization can be performed when it is reasonably certain that a woman is no longer pregnant.

Strength of recommendation: Strong

Quality of evidence: Very low

Last reviewed: May 29, 2013

Fertility return

If a woman desires contraception after a medical abortion, she should begin her method of choice as soon as possible. On average, a woman will ovulate within 20 days of a medical abortion with mifepristone and misoprostol, but can ovulate in as little as eight days (Schreiber, Sober, Ratcliffe & Creinin, 2011). Therefore, all women who wish to delay conception should leave the facility with an effective method of contraception. If a woman desires long-acting contraception or sterilization but it cannot be provided, she should get an interim method and be referred to the appropriate facility.

Contraceptive start

Most forms of contraception (including pills, injections and implants) may be started with the first pill of a medical abortion as long as there are no medical contraindications (WHO, 2009). IUDs may be inserted and sterilization performed as soon as it is reasonably certain that a woman is no longer pregnant (WHO, 2012).

Combined oral contraceptives: Two randomized controlled trials of combined oral contraceptive pills started immediately after medical abortion compared to placebo showed that pills do not have a significant effect on the efficacy of medical abortion or the quantity or duration of blood loss (Tang, Gao, Cheng, Lee, & Ho, 1999; Tang, Xu, Cheng, Lee, & Ho, 2002).

Intrauterine device: IUDs inserted within five to ten days of a successful medical abortion have low rates of expulsion and high continuation (Betstadt, Turok, Kapp, Feng & Borgatta, 2011; Sääv, Stephansson & Gemzell-Danielsson, 2012). IUD insertion one week after medical abortion has higher uptake and lower pregnancy rates than delayed insertion without an increased risk of expulsion (Shimoni, Davis, Ramos, Rosario & Westhoff, 2011; Saav, et al., 2012).

Natural family planning: Natural family planning, or the fertility-awareness method, should only be used after a woman has had at least one postabortion menses and only if she had regular menstrual cycles prior to the abortion (WHO, 2009).

Barrier methods: Barrier methods are safe to use at any time after a first-trimester medical abortion and can be

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used as a bridge to long-term methods or sterilization.

Sterilization: Sterilization may be performed as soon as it is reasonably certain that a woman is no longer pregnant and that a woman is not unduly influenced by the circumstances surrounding her abortion (WHO, 2012).

Quality of the evidence

There is limited clinical data to support the recommendation to start hormonal methods on the same day as the first pill of medical abortion. This recommendation is based on expert opinion (WHO, 2012). A woman's immediate need for reliable contraception after medical abortion, coupled with the risk that delayed contraceptive provision reduces uptake, strongly supports the recommendation to start these methods immediately.

Young women

The IUD for women under the age of 20 is classified by WHO as category two, in which the benefits generally outweigh the risks. While risk is slightly increased due to higher rates of sexually transmitted infections and expulsion in this patient population, IUDs are still a safe, effective and recommended method for women under the age of 20. Sterilization may be performed, but a young woman will need special precautions due to the increased risk of regret (WHO, 2009).

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First-trimester medical abortion with mifepristone and misoprostol: Home use of abortion medications

Recommendation:

- Women may take mifepristone in a facility or at home when it is convenient for them to start the abortion regimen.
- Home use of misoprostol in a combined regimen of mifepristone and misoprostol is a safe option for women with pregnancies below nine weeks (63 days) gestation (WHO, 2012). In some settings, home use of buccal misoprostol 800mcg may be offered through 10 weeks (70 days) gestation.

Strength of recommendation: Strong

Quality of evidence:

Up to 63 days: High

64-70 days: Low

Last reviewed: May 30, 2013

Background

Traditionally, providers have given mifepristone to women to take in a facility to start the abortion regimen. Twenty-four to 48 hours later, women may take misoprostol in a medical facility, their own home or another safe location. Because of women's individual preferences for privacy, support and timing, they should have options about the location of mifepristone and misoprostol use.

Home use of mifepristone

A prospective nonrandomized multicenter cohort study of 301 women showed that half of women who were offered home or facility use of mifepristone chose home use (Swica et al., 2012). Women who used mifepristone at home did not have any difference in success rates, telephone calls or emergency room visits and were highly satisfied. The most common reason for electing home use was for flexibility in scheduling the abortion.

Home use of misoprostol up to 63 days

A systematic review of nine prospective comparative cohort studies with 4,522 women up to 56 days gestation showed that complete abortion rates and adverse events rate were the same for home- or facility-based misoprostol use (Ngo, Park, Shakur, & Free, 2011). Women in the included studies found home use as acceptable as clinic use. Large observational cohorts up to 63 days also confirm the safety and efficacy of home use of misoprostol (Cleland, Creinin, Nucatola, Nshom, & Trussell, 2013; Goldstone, Michelson, & Williamson, 2012). The World Health Organization, American College of Obstetricians and Gynecologists and Royal College of Obstetricians and Gynaecologists recommend home use of misoprostol up to 63 days (ACOG, 2005; RCOG, 2011; WHO, 2012).

Home use of misoprostol from 64 to 70 days

A United States multi-center study of 729 women in the United States comparing a single dose of buccal

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misoprostol 800mcg at home from 57 to 63 days and 64 to 70 days showed no difference in success rates, ongoing pregnancy or adverse events (Winikoff et al., 2012). Offering women up to 10 weeks gestation a single dose of buccal misoprostol at home rather than repeat doses of misoprostol in a facility may be appropriate in some settings (Boersma, Meyboom-de Jong, & Kleiverda, 2011; Winikoff, et al., 2012). This study used ultrasound to determine gestational age for eligibility. Programs using this approach in different conditions should monitor their results to ensure success in their settings.

Young women

This recommendation is the same for young women as for adult women.

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Misoprostol product quality

Recommendation:

Because different misoprostol products have varying quality and can degrade over time, providers should track medical abortion success rates to ensure that they are using an effective product. Providers should store misoprostol in a cool dry place.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: June 6, 2013

Background

With the increasing use of misoprostol for reproductive health indications, there are concerns about the quality of misoprostol products. If misoprostol degrades, it may lead to decreased success rates with medical abortion and unsuccessful treatment of incomplete abortion and postpartum hemorrhage. A technical memo distributed by Pathfinder International reported that Misotac, a brand of misoprostol manufactured by Sigma, was recalled because batches of the medicine had degraded and no longer contained a sufficient amount of the active ingredient (Pathfinder, 2011).

Differences in quality related to manufacturing

There are at least 30-40 manufacturers of misoprostol worldwide and some manufacturers subcontract, which makes it difficult to enforce Good Manufacturing Practice and ensure quality across all brands (Hall, 2011). Although misoprostol is thought to be stable at normal room temperature, the active pharmaceutical ingredient (misoprostol oil) used in manufacturing must be stored below -20°C. Thus, exposure to heat and humidity during manufacturing, packaging and storage may compromise the quality of misoprostol (Cayman Chemical, 2012).

A 2011 study analyzed 76 misoprostol samples from countries all over the world (Hall, 2011). Two types of misoprostol contained the drug diclofenac and were excluded from analysis. When the remaining 74 samples were tested for content and purity, eight of the 200mcg tablets contained less than 40mcg of active ingredient. The analysis found that three factors influenced misoprostol integrity: 1) impact of moisture at all stages 2) manufacture and quality of the active pharmaceutical ingredient and 3) packaging. Misoprostol that was packaged in double-aluminum blister packs (aluminum on top and bottom) was found to retain the most active ingredient.

Misoprostol brands that have been approved by the European Union or the United States Food and Drug Administration are known to conform to Good Manufacturing Practice and are high quality. The United Nations Population Fund (UNFPA) has added misoprostol to its list of commodities which are available through long-term agreement. UNFPA is committed to procuring products which meet specified requirements and standards, according to internationally recognized quality standards.

Clinic use and storage

Even misoprostol manufactured in high-quality conditions and packaged well can become inactive if it is shipped or stored in conditions that expose it to heat or humidity for prolonged periods of time. There have not been large

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field studies on the stability of misoprostol in tropical climates, but laboratory studies show that misoprostol is less stable when exposed to moisture or heat (Chu, Wang, Pang & Rogers, 2007; WHO, 2009). Even in normal room temperature conditions (25°C and 60 percent humidity), when providers cut blister packs to distribute tablets, if the packaging on the remaining stored tablets is inadvertently opened, the tablets' potency degrades within 48 hours and continues to degrade over time (Berard & Fiala, 2012).

Quality assurance

If providers notice a sudden decrease in medical abortion success rates from expected baseline, they should discard the lot of misoprostol being used and start a new lot. Providers should consult with each other to determine which local misoprostol brands are most effective. Store misoprostol in dry conditions at temperatures at or below 25°C (77°F) (Pfizer, 2002).

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First-trimester medical abortion with mifepristone and misoprostol or misoprostol only: Ultrasound findings at follow-up

Recommendation:

Ultrasound is not necessary for medical abortion follow-up and may lead to unnecessary intervention. If clinicians choose to use ultrasound, the only ultrasound finding that requires intervention is an ongoing viable pregnancy.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 30, 2013

Background

Ultrasound is not necessary to provide abortion care (WHO, 2012) but may be common in some settings. Ultrasound for follow-up after medical abortion has diagnostic limitations. Except for the rare case of an ongoing viable pregnancy, intervention after a medical abortion should be based on clinical symptoms and not ultrasound findings.

Findings

Endometrial thickening: After a successful medical abortion, the endometrium can have varying thickness and have a complex or heterogeneous appearance.



Courtesy of Mary Fjerstad

Endometrial thickening

Multiple retrospective and prospective cohort studies have shown that endometrial thickness has a wide range in women after medical abortion, with significant overlap between women with successful and failed medical abortion (Cowett, Cohen, Lichtenberg & Stika, 2004; Markovitch, Tepper, Klein, Fishman & Aviram, 2006; Parashar, Iversen, Midbøe, Myking & Bjørge, 2007; Rørbye, Nørgaard & Nilas, 2004). In a pooled analysis of 2,208 women one week after medical abortion, once women with a persistent gestational sac were excluded, the average endometrial thickness was 10.9mm in women who did not require more intervention and 14.5mm in

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thirty women who did (Reeves, Fox, Lohr & Creinin, 2009). Although the average endometrial thickness in women who require intervention tends to be higher, because of the range and overlap between successful and unsuccessful abortion, no study has found that there is a thickness above which a diagnosis of unsuccessful medical abortion can be made. The decision of whether to intervene should be made on clinical signs and symptoms, such as ongoing or heavy bleeding, rather than ultrasound findings.

Persistent gestational sac: A persistent gestational sac, in which the sac is present but there is no viable embryonic tissue, occurs in less than one percent of medical abortions with the recommended mifepristone and misoprostol regimen (Creinin et al., 2004; Creinin et al., 2007; Winikoff et al., 2008). A persistent gestational sac is not a viable pregnancy and may be managed with aspiration, a second dose of misoprostol or expectant management according to a woman's preference. In a study of women with a persistent gestational sac within 11 days of medical abortion, a second dose of misoprostol was found to lead to expulsion of a nonviable sac in 69 percent of women (Reeves, Kudva, & Creinin, 2008).



Persistent gestational sac

Ongoing viable pregnancy: An ongoing pregnancy, in which the sac and an embryo with cardiac activity are present, occurs in less than one percent of medical abortions with the recommended mifepristone and misoprostol regimen (Von Hertzen et al., 2009; Winikoff, et al., 2008). Some women will be able to identify this outcome without ultrasound due to lack of bleeding or continued pregnancy symptoms. A woman with an ongoing pregnancy should be offered uterine evacuation as soon as possible. She may have vacuum aspiration, or a second dose of misoprostol may be considered. The success rate of misoprostol after failed medical abortion is 36 percent (Reeves, Kudva & Creinin, 2008; WHO, 2012). If a woman chooses a second dose of misoprostol, she must be followed to see if it is successful.

Young women

This recommendation is the same for young women as it is for adult women.

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First-trimester medical abortion with mifepristone and misoprostol or misoprostol only: Risk of fetal malformations after exposure to mifepristone and misoprostol

Recommendation:

Exposure to mifepristone alone has not been shown to cause fetal malformations. Exposure to misoprostol, whether in a combined or misoprostol-only regimen, carries a small increased risk of malformations if the woman has an ongoing pregnancy and decides not to terminate. Women with an ongoing pregnancy after using misoprostol should be counseled about the risk if they choose to carry the pregnancy to term.

Strength of recommendation: Strong

Quality of evidence: Mifepristone: Very low

Misoprostol: Moderate

Last reviewed: May 21, 2013

Background

The expected rate of malformations in the general population is approximately three percent (Dolk, Loane, & Garne, 2010). Exposure to certain medications, infections, radiation or drugs of abuse during embryonic or fetal development may result in an increased risk of malformations if the pregnancy continues.

Mifepristone

Mifepristone exposure may occur if a woman changes her mind and does not take misoprostol after taking mifepristone. Data on continuing pregnancy after mifepristone exposure without misoprostol are limited. The largest prospective study of 46 women continuing a pregnancy after mifepristone only resulted in eight miscarriages and two major malformations in the pregnancies that continued (5.3 percent). Both malformations were not thought to be related to mifepristone exposure but may have been a result of other medical conditions (Bernard et al., 2013).

Misoprostol

The association between misoprostol and congenital anomalies is better established. Case reports, cohort studies (da Silva Dal Pizzol, Tierling, Schüler-Faccin, Sanseverino & Mengue, 2005; Vauzelle, Beghin, Cournot & Elephant, 2013) and case-control studies (da Silva Dal Pizzol, Knop & Mengue, 2006) show that the incidence of malformations peaks if misoprostol is used between five and eight weeks after a woman's last menstrual period (LMP) and is not associated with anomalies after 13 weeks LMP (Philip, Shannon & Winikoff, 2002). The most typical malformations associated with misoprostol use are Möbius sequence, a rare disorder of cranial nerve

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palsies associated with limb anomalies and craniofacial defects, and terminal transverse limb defects (da Silva Dal Pizzol, et al., 2006). Although not clearly established, the proposed mechanism is vascular disruption from uterine contractions leading to disordered fetal development (Gonzalez et al., 2005; Shepard, 1995).

A systematic review of four case-control studies with 4,899 cases of congenital anomalies and 5,742 controls showed an increased rate of misoprostol exposure in cases with anomalies (OR 3.56, 95% CI 0.92-12.98) (da Silva Dal Pizzol, et al., 2006). Misoprostol exposure was 25 times more likely in cases with Möbius sequence and 12 times more likely with terminal transverse limb defects. A prospective follow-up study comparing women who used misoprostol before 12 weeks of pregnancy to women who used antihistamines showed that the rate of fetal malformations was higher in the 236 pregnancies exposed to misoprostol (4%) than in 255 controls (1.8%) although the finding was not statistically significant (OR=2.2, 95% CI = 0.6-7.7) (Vauzelle, et al., 2013). Three malformations (2%) in the misoprostol group were consistent with misoprostol-related anomalies.

Although the rate of misoprostol exposure is higher in children born with characteristic defects such as Möbius sequence, because the anomalies are so rare the overall risk that a woman who takes misoprostol in the first trimester and carries a pregnancy to term will have a child born with a malformation related to misoprostol exposure is low. A woman's risk of a malformation related to misoprostol exposure is less than 10 per 1,000 exposures (Philip, et al., 2002).

Young women

This recommendation is the same for young women.

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First-trimester medical abortion with mifepristone and misoprostol: Contraindications and precautions

Recommendation:

Contraindications:

- Previous allergic reaction to one of the drugs involved
- Inherited porphyria
- Chronic adrenal failure
- Known or suspected ectopic pregnancy

Precautions:

- IUD in place. Evaluate for the presence of ectopic pregnancy. If none, remove the IUD.
- Severe uncontrolled asthma or long-term corticosteroid therapy. No evidence exists regarding use of mifepristone in steroid-dependent women. Providers must use clinical judgment if no other alternatives to safe abortion exist. Increase steroid dose for three to four days and monitor the woman very closely. Conditions such as poorly controlled asthma may still be worsened.
- Severe/unstable health problems including but not limited to hemorrhagic disorders, heart disease, and severe anemia. No evidence exists on the use of medical abortion in women with hemorrhagic disorder, heart disease, severe anemia or severe/unstable health problems. Whether to provide medical abortion to women with these conditions will depend on the available options for safe abortion care, referrals, and clinical judgment. If medical abortion is provided, it should be given under close observation.

Strength of recommendation: Moderate

Quality of evidence: The quality of the evidence is graded for each specific contraindication or precaution below

Last reviewed: May 30, 2013

Definitions

Contraindications: If a woman has these specific conditions, under no circumstances should she be offered medical abortion with mifepristone and misoprostol. Vacuum aspiration should be considered or she should be referred to a facility where she can be offered alternate care.

Precautions: If a woman has these specific conditions, medical abortion with mifepristone and misoprostol has higher risks than normal. The risks, benefits and alternatives to medical abortion must be considered. Medical abortion provision may require a higher degree of clinical judgment, skill and monitoring. Referral to a higher-level facility may be appropriate.

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Quality of evidence:

Contraindications

Previous allergic reaction to one of the drugs involved

Allergic reactions have been reported after the use of mifepristone and misoprostol (Hauseknecht, 2003).

Quality of evidence: High

Inherited porphyria

Porphyrias are rare metabolic disorders in which enzymes in heme are deficient. Theoretically, mifepristone could exacerbate porphyria (Ventura et al., 2009).

Quality of evidence: Low. No human studies exist, but animal models exhibit the effect of mifepristone (Cable et al., 1994).

Chronic adrenal failure

Mifepristone is a glucocorticoid receptor antagonist (Spitz & Bardin, 1993). Mifepristone blocks negative feedback mechanisms that control cortisol secretion. In women with adrenal insufficiency on long-term corticosteroid therapy, mifepristone exposure may exacerbate the underlying condition (Sitruk-Ware & Spitz, 2003).

Quality of evidence: Low. There are no data on mifepristone use in pregnant women with adrenal insufficiency, but there is experimental and animal data to support the recommendation.

Known or suspected ectopic pregnancy

Mifepristone and misoprostol do not treat ectopic pregnancy, and use of the medications may delay diagnosis of this life-threatening condition.

Quality of evidence: High

Precautions

IUD in place

A woman who is pregnant with an IUD in place is at significantly elevated risk of ectopic pregnancy (Barnhart, 2009). The woman must be evaluated for the presence of ectopic pregnancy. If negative, the IUD should be removed before starting medical abortion due to the theoretical risk of uterine perforation from contractions during medical abortion and the potential risk of infection (Danco, 2010; Davey, 2006).

Quality of evidence: Low. There are no studies to verify whether having an IUD in place poses actual risks during medical abortion.

Severe uncontrolled asthma or long-term corticosteroid therapy

Mifepristone is a glucocorticoid receptor antagonist (Spitz & Bardin, 1993). Mifepristone blocks negative feedback mechanisms that control cortisol secretion. In women on long-term corticosteroid therapy for severe or uncontrolled asthma, mifepristone exposure may exacerbate the underlying condition (Sitruk-Ware & Spitz, 2003). There are no direct studies of medical abortion among women on corticosteroid treatment, but one review suggested that increasing the dose of the steroid medications can counteract the cortisol blunting effect of mifepristone (Davey, 2006). For most conditions, adjusting the dose of corticosteroid medications after mifepristone administration and careful monitoring may allow for medical abortion.

Medical abortion in asthmatic women requiring systemic corticosteroids has not been studied. One review

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suggests using a high level of caution when giving mifepristone to such women and only doing so if the asthma is well controlled (Davey, 2006). The glucocorticoid dose should be increased for several days before and after mifepristone. Other experts recommend that women with severe, poorly controlled asthma who are on long-term corticosteroids not take mifepristone due to the life-threatening nature of acute asthma exacerbation (Christin-Maitre et al., 2000; Creinin & Gemzell Danielsson, 2009; Sitruk-Ware, 2006). Giving mifepristone to such women risks exacerbating asthma.

Inhaled corticosteroids for asthma are not systemically absorbed and are not a contraindication to mifepristone. Some experts recommend that mifepristone and misoprostol should be available to women with asthma as long as they are not on long-term systemic steroids (Creinin & Gemzell Danielsson, 2009).

Quality of evidence: Moderate

Severe medical problems

Medical abortion studies tend to exclude women with severe anemia or severe medical problems (Christin-Maitre et al., 2000; Sitruk-Ware & Spitz, 2003). Whether to provide medical abortion to women with these conditions will depend on clinical judgment, monitoring and options available for safe abortion care.

Quality of evidence: Low

Young women

The contraindications and precautions for medical abortion with mifepristone and misoprostol are the same in young women as they are in adult women.

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First-trimester medical abortion with mifepristone and misoprostol: Recommended regimen

Recommendation:

- **Up to nine weeks gestation:** Mifepristone 200mg orally followed 24-48 hours later by misoprostol 800mcg buccally, sublingually or vaginally.
- **9 to 10 weeks gestation:** Mifepristone 200mg orally followed 24-48 hours later by misoprostol 800mcg buccally.
- **10 to 13 weeks gestation:** Mifepristone 200mg orally followed 36-48 hours later by misoprostol 800mcg vaginally then 400mcg vaginally or sublingually every three hours for a maximum of five doses of misoprostol.

Strength of recommendation: Strong

Quality of evidence:

- **Up to nine weeks:** Moderate
- **9 to 10 weeks:** Low
- **10 to 13 weeks:** Low

Last reviewed: May 21, 2013

Up to nine weeks:

Multiple randomized controlled clinical trials have shown that the combination of mifepristone and misoprostol is an effective medical abortion regimen with success rates ranging from 95 to 98 percent (Kulier et al., 2011; Raymond, Shannon, Weaver, & Winikoff, 2012). Vaginal, buccal and sublingual misoprostol are more effective than oral misoprostol (Kulier et al., 2011). Buccal (Middleton et al., 2005) and sublingual (Tang, Lau, Ng, Lee, & Ho, 2003; von Hertzen et al., 2010) dosing have higher rates of gastrointestinal side effects than vaginal dosing. Sublingual dosing is associated with more side effects than buccal dosing (Chai, Wong, & Ho, 2012). In some settings, buccal or sublingual dosing may be preferred due to infection prevention (Fjerstad et al., 2009), legal restrictions or a woman's preference.

9 to 10 weeks:

Evidence is rapidly evolving. The above recommendation is based on one study, a United States multi-center trial of 729 women using mifepristone in a clinic and misoprostol 800mcg buccally at home. There was no difference in successful abortion and ongoing pregnancy in women between eight to nine weeks compared to 9 to 10 weeks (Winikoff et al., 2012). Overall, the successful abortion rates were 93 percent with ongoing pregnancy rates of 3 percent in both groups. Offering women up to 10 weeks gestation a single dose of buccal misoprostol at home rather than repeat doses of misoprostol in a facility may be appropriate in some settings (Boersma, Myboom-de Jong & Kleiverda, 2011; Winikoff et al., 2012). This study used ultrasound to determine gestational age for eligibility. Programs using this approach in different conditions should monitor their results to ensure success in their settings.

10 to 13 weeks

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A cohort study of 1,076 women showed a combination of mifepristone and repeat doses of misoprostol is safe and effective between nine and 13 weeks (Hamoda, Ashok, Flett & Templeton, 2005). All women took misoprostol in the health facility. The success rate for this regimen was high at 95.8 percent with a low rate of serious adverse events. Repeat dosing of misoprostol has been shown to increase the efficacy of second-trimester medical abortion and may be used for women in the late first trimester (Wildschut et al., 2011).

Young women

The regimen for medical abortion with mifepristone and misoprostol in the first trimester is the same in young women as in adult women.

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First-trimester medical abortion with mifepristone and misoprostol: Confirmation of success

Recommendation:

- Most women can confirm a successful medical abortion with mifepristone and misoprostol.
- Providers may perform a bimanual exam to assist in the confirmation of successful abortion.
- Ultrasound or other testing is needed only in cases where the diagnosis is unclear.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 30, 2013

Woman's assessment of successful abortion

Women can accurately assess whether their medical abortion with mifepristone and misoprostol was successful. In multiple studies, women who believed that they had a successful abortion were correct over 99 percent of the time (Cameron, Glasier, Dewart, Johnstone, & Burnside, 2012; Jackson, Dayananda, Fortin, Fitzmaurice, & Goldberg, 2012; Perriera et al., 2010; Rossi, Creinin, & Meyn, 2004). Routine follow-up after medical abortion with mifepristone and misoprostol is not needed (WHO, 2012).

Bimanual exam

Providers may help confirm successful abortion at a follow-up visit by reviewing a patient history and performing a bimanual exam. In one study of 931 women following up after medical abortion in which providers reviewed a woman's history and performed a bimanual exam, the providers were able to identify successful abortion in over 99 percent of cases (Rossi et al., 2004).

Ultrasound

Ultrasound can be used to confirm successful abortion but is not necessary and can add to the cost and complexity of medical abortion (Kaneshiro, Edelman, Sneeringer, & Ponce de Leon, 2011). Ultrasound is helpful in cases where there is doubt about whether the abortion has been successful.

Serum pregnancy testing

Serum pregnancy testing has been used as an alternative to ultrasound to diagnose successful medical abortion and compares favorably to ultrasound in reducing interventions at the time of follow-up (Clark, Panton, Hann & Gold, 2007; Dayananda, Maurer, Fortin & Goldberg, 2013; Fiala, Safar, Bygdeman & Gemzell-Danielsson, 2003). Serum pregnancy testing is only useful when a pre-treatment hCG has been obtained for comparison. The utility of serum pregnancy testing is low in areas where access to laboratory testing is limited.

Urine pregnancy testing

A negative urine pregnancy test is usually reassuring that an abortion has been successful; however, it is rare, but does occur, that a pregnancy test is negative but a woman is still pregnant (false negative). Urine pregnancy tests

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often have positive results even when the medical abortion has been successful (false positive) (Cameron et al., 2012; Clark et al., 2010; Godfrey, Anderson, Fielding, Meyn, & Creinin, 2007; Perriera et al., 2010). Due to the high rate of false positive results, urine pregnancy testing is not recommended for routine confirmation of success.

Young women

The recommendation for follow-up after first-trimester medical abortion is the same for young women as it is for adult women.

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First-trimester medical abortion with misoprostol only: Contraindications and precautions

Recommendation:

Contraindications:

- Previous allergic reaction to misoprostol.
- Known or suspected ectopic pregnancy.

Precautions:

- Intrauterine device (IUD) in place. Evaluate for the presence of ectopic pregnancy. If none, remove the IUD.
- Severe/unstable health problems including but not limited to hemorrhagic disorders, heart disease and severe anemia. No evidence exists on the use of medical abortion in women with hemorrhagic disorder, heart disease, severe anemia or severe/unstable health problems. Whether to provide medical abortion to women with these conditions will depend on the available options for safe abortion care, referrals, and clinical judgment. If medical abortion is given, it should be under close observation.

Strength of recommendation: Moderate

Quality of evidence: The quality of the evidence is graded for each specific contraindication or precaution below.

Last reviewed: May 30, 2013

Definitions

Contraindications: If a woman has these specific conditions, under no circumstances should she be offered medical abortion with misoprostol only. Vacuum aspiration should be considered or she should be referred to a facility where she can be offered alternate care.

Precautions: If a woman has these specific conditions, medical abortion with misoprostol only has higher risks than normal. The risks, benefits and alternatives to medical abortion must be considered. Medical abortion provision may require a higher degree of clinical judgment, skill and monitoring. Referral to a higher-level facility may be appropriate.

Contraindications

Previous allergic reaction to misoprostol:

Allergic reactions have been reported after the use of misoprostol (Hausknecht, 2003).

Quality of evidence: High

Known or suspected ectopic pregnancy:

Misoprostol does not treat ectopic pregnancy and use of the medications may delay diagnosis of this life-

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threatening condition.

Quality of evidence: High

Precautions

IUD in place:

A woman who is pregnant with an IUD in place is at significantly elevated risk of ectopic pregnancy (Barnhart, 2009). The woman must be evaluated for the presence of ectopic pregnancy. If negative, the IUD should be removed before starting medical abortion due to the theoretical risk of uterine perforation from contractions during medical abortion and the potential risk of infection (Danco, 2010; Davey, 2006). There are no studies to verify whether having an IUD in place poses actual risks during medical abortion.

Quality of evidence: Low. There are no studies to verify whether having an IUD in place poses actual risks during medical abortion.

Severe/unstable health problems:

Medical abortion studies tend to exclude women with severe anemia or severe medical problems (Christin-Maitre, Bouchard & Spitz, 2000; Sitruk-Ware, 2006) Whether to provide medical abortion to women with these conditions will depend on clinical judgment, monitoring and options available for safe abortion care.

Quality of evidence: Low

Young women

The contraindications and precautions for medical abortion with misoprostol only are the same in young women as in adult women.

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First-trimester medical abortion with misoprostol only: Recommended regimen

Recommended regimen up to 13 weeks:

Dose	Route	Timing
Misoprostol 800mcg (four 200mcg pills)	Vaginal	Every three to 12 hours for a maximum of three doses
Misoprostol 800mcg (four 200mcg pills)	Sublingual	Every three hours for a maximum of three doses

Strength of recommendation: Strong

Quality of evidence:

- Up to nine weeks: Moderate
- Nine through 13 weeks: Low

Last reviewed: May 21, 2013

Success of misoprostol-only medical abortion

The success rate of medical abortion with misoprostol only is around 85 percent (von Hertzen et al., 2007). Misoprostol-only treatment should be considered when mifepristone is not available. In general, misoprostol-only regimens have higher rates of success at lower gestational age (von Hertzen et al., 2007; Zikopoulos et al., 2002), with higher numbers of doses (Carbonell, Varela, Velazco, Tanda, & Sanchez, 1999) and with longer follow-up times (Bugalho, Mocumbi, Faundes, & David, 2000). However, women's satisfaction decreases the longer the abortion process lasts (Ngai, Tang, Chan, & Ho, 2000).

Misoprostol-only abortion up to nine weeks

The only multicenter randomized controlled trial to compare different misoprostol-only dosing intervals showed that complete abortion rates are equivalent when misoprostol is given vaginally every three to twelve hours or sublingually every three hours for three doses. Sublingual dosing had a higher incidence of side effects than vaginal dosing (von Hertzen et al., 2007).

Misoprostol-only abortion between nine and 13 weeks

There is scant evidence to recommend an appropriate dosing regimen between nine and 13 weeks. The only direct evidence for this gestational age comes from three small cohort studies where misoprostol 800mcg was given vaginally every 12 or 24 hours for up to three doses (Carbonell Esteve et al., 1998; Carbonell et al., 1999; Carbonell et al., 2001). However, there is strong evidence in randomized controlled trials of misoprostol-only in the early second trimester that support using a vaginal dosing interval of every three hours over 13 weeks (von Hertzen et al., 2009). Given the evidence supporting repeat doses of sublingual or vaginal misoprostol below nine and above 13 weeks, the evidence-based regimen for below nine weeks may be used between nine and 13 weeks.

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The recommended regimen for first-trimester medical abortion with misoprostol only is the same for young women as for adult women.

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Second-trimester abortion, dilatation and evacuation and medical abortion: Comparing methods

Recommendation:

- Dilatation and evacuation (D&E) and medical abortion (MA) with mifepristone and misoprostol or misoprostol only are safe and effective methods of second-trimester abortion (WHO, 2012).
- MA has a higher rate of retained products and failed initial method and minor adverse events.
- Significant adverse events do not differ between the two methods.
- D&E requires a trained, experienced provider and specialized equipment.
- When both methods are available and a woman is eligible, she should be allowed to choose the method that is appropriate for her.

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: June 5, 2013

Comparison of methods

In retrospective cohort studies, women in the second trimester who have medical abortion (MA) compared to dilatation and evacuation (D&E) have an increased rate of failed abortion and retained products of conception with a need for further intervention (Autry, Hayes, Jacobson & Kirby, 2002; Bryant, Grimes, Garrett, & Stuart, 2011). The rate of major adverse events including infection, transfusion, hysterectomy and death is not increased.

The largest randomized trial of second-trimester abortion methods included 122 women and showed a similar rate of complications between D&E and MA with mifepristone and misoprostol (Kelly, Suddes, Howel, Hewison & Robson, 2010). However, women randomized to MA had more bleeding and pain and were less satisfied than women who had D&E. A pilot randomized trial of 18 women comparing D&E and MA with misoprostol only had a higher rate of adverse events in the women undergoing MA (Grimes, Smith, & Witham, 2004). Both randomized trials had difficulty with recruitment due to women's strong preferences for one type of procedure over another.

In published studies of MA compared to D&E, rates of intervention for MA may be artificially high because failed MA was defined as no delivery within 24 hours (Bryant, et al., 2011) and retained placenta was diagnosed after two hours (Grimes, et al., 2004). In practice, more time may be allowed for successful MA to occur.

The importance of choice

In settings where D&E and MA are available, if a woman is a candidate for either procedure, she should be offered a choice. A study of women undergoing second-trimester abortions for fetal abnormalities demonstrated that when women chose whether to undergo D&E or MA, their rates of post-procedure depression did not differ (Burgoine et al., 2005). Choice of methods is very individual – some women prefer the speed, predictability and comfort of D&E, while others prefer a more “labor-like” process with an intact fetus (Kelly, et al., 2010; Kerns, et al., 2012). Some women may want to see or hold an intact fetus while others prefer not to. In some cases, an intact fetus may allow for a more comprehensive fetal autopsy where it is needed.

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Young women

The recommendation is the same for young women as for older women.

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Second-trimester medical abortion and dilatation and evacuation (D&E): Gestational dating

Recommendation:

Accurate assessment of gestational age is important for second-trimester abortion services, especially when dilatation and evacuation is used. Gestational age can be estimated by a woman's report of her last menstrual period (LMP) and a physical exam. Ideally, ultrasound should be used to confirm the duration of pregnancy.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: June 5, 2013

Background

Errors in gestational dating can increase the risks associated with second-trimester abortion. In facilities using dilatation and evacuation (D&E), if gestational age is underestimated, providers may not have the experience and equipment to complete the procedure safely. Accurate assessment of gestational age may help providers and women choose a safer procedure or indicate the need for referral to another facility.

Dating

There is no evidence to recommend the most appropriate way to confirm gestational age in the second trimester. In the United States, 99 percent of providers use ultrasound in the second trimester, but data is lacking from international sites (O'Connell, Jones, Lichtenberg, & Paul, 2008).

Ideally, providers should use ultrasound to confirm the duration of the pregnancy and also use the date of the last menstrual period and pelvic exam to check size, consistency and position of the uterus. A single biparietal diameter is a simple and accurate method to confirm gestational age (Goldstein & Reeves, 2009). A femur length measurement can be used to confirm the biparietal diameter or used if there are technical difficulties in obtaining a biparietal measurement.

In settings where it is not possible to confirm gestational age by ultrasound, it is extremely important that staff be adequately trained in pregnancy dating. After the abortion, clinicians can confirm gestational age by comparing actual fetal measurements (fetal foot length) to the expected gestational age (Drey, Kang, McFarland, & Darney, 2005). This comparison gives the clinicians feedback regarding the accuracy of their pre-procedure dating estimates.

Young women

This recommendation is the same for young women as for adult women.

References

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Second-trimester medical abortion and dilatation and evacuation (D&E): Induced fetal demise

Recommendation:

Induced fetal demise prior to second-trimester medical abortion or dilatation and evacuation (D&E) does not increase the safety of abortion and is not recommended for medical indications. There may be legal or ethical indications for inducing fetal demise.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: June 5, 2013

Background

Some providers use induced fetal demise prior to second-trimester medical abortion or dilatation and evacuation (D&E). In some cases, patients, providers or staff may prefer that fetal demise occurs before an abortion procedure (Jackson, Teplin, Drey, Thomas & Darney, 2001). Before medical abortion, induced fetal demise can prevent transient fetal survival. Although the rate of complications in women with digoxin injection may be acceptably low in some published case series (Steward, Melamed, Kim, Nucatola & Gatter, 2012), there is no current evidence that shows a medical benefit for the practice.

Evidence related to induced fetal demise

D&E: A randomized, controlled trial of induced fetal demise with digoxin prior to D&E which compared digoxin to saline injection showed no benefit to digoxin and an increased rate of vomiting (Jackson et al., 2001). A retrospective cohort study comparing women with digoxin injection prior to D&E with historical controls showed an increase in complications including more hospital admissions, extramural deliveries, and infections in women who had digoxin (Dean et al., 2012).

Medical abortion: There are no trials to evaluate the safety and efficacy of induced fetal demise before medical abortion with the currently recommended second-trimester regimens.

Technique

Fetal demise can be achieved prior to a second-trimester abortion by injecting either potassium chloride directly into the fetal heart or digoxin into the fetus or amniotic fluid or interrupting the fetal umbilical cord.

Potassium chloride: Potassium chloride injection requires skill in ultrasound guidance techniques and has more potential risk from maternal intravascular injection including cardiac arrest (Borgatta & Kapp, 2011; Coke, Baschat, Mighty & Malinow, 2004). It is not recommended in a low-resource setting.

Digoxin: In a pharmacokinetic study of eight women who had intra-amniotic injection of digoxin 1mg prior to second-trimester D&E, maternal serum digoxin levels were in the low therapeutic range and were not associated with cardiac changes (Drey, Thomas, Benowitz, Goldschlager & Darney, 2000). A pilot randomized trial of

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intraamniotic or intrafetal digoxin at doses of 1mg or 1.5mg showed an overall rate of fetal demise of 87 percent with no difference in efficacy based on the dose or route of administration (Nucatola, Roth & Gatter, 2010). To be effective, digoxin intra-amniotic injection should be performed one to two days before the planned abortion procedure.

Interruption of the fetal cord: During second-trimester D&E or medical abortion when the fetus is in breech presentation, fetal demise can be caused by interrupting the umbilical cord.

Young women

This recommendation is the same for young women as for adult women.

References

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Second-trimester dilatation and evacuation or medical abortion: Contraception

Recommendation:

Immediate initiation of hormonal and non-hormonal contraception following second-trimester dilatation and evacuation (D&E) or medical abortion is encouraged and considered safe.

Strength of recommendation: Strong

Quality of evidence:

- **Intrauterine Device after D&E:** Moderate
- **Other contraceptive methods:** Low

Last reviewed: May 29, 2013

Contraceptive methods other than intrauterine device (IUD)

Although the immediate use of most methods of contraception has not been formally studied following second-trimester abortion, because of the demonstrated safety of contraception after first-trimester vacuum aspiration and medical abortion, the World Health Organization (WHO) categorizes the immediate initiation of hormonal injections, implants, combined hormonal contraception (pills, patches and rings) and progestin-only pills as category 1, or safe for use.

IUD

A Cochrane meta-analysis of 11 trials of immediate postabortal IUD following surgical abortion use concluded that although expulsion rates may be higher with immediate placement, continuation is higher with no increase in complications (Grimes, Lopez, Schulz, & Stanwood, 2010). In two randomized controlled trials of immediate versus delayed IUD placement after second-trimester D&E, rates of IUD use are significantly higher with immediate insertion, with no increase in infection or complication rates (Cremer et al., 2011; Hohmann et al., 2012). Expulsion rates for women who had immediate insertion in both studies were low (3.1 percent and 6.8 percent) and were the same as delayed insertion.

Notably, in both of these studies, about half of women randomized to delayed insertion did not come back to have the IUD inserted. Requiring a follow-up visit for IUD insertion is a significant barrier to obtaining the IUD (Stanek, Bednarek, Nichols, Jensen & Edelman, 2009). No studies exist of IUD placement immediately following second trimester medical abortion and the WHO Medical Eligibility Criteria recommendations do not differ based on the type of abortion performed. Although not directly translatable, the evidence from post-partum IUD insertion is reassuring (Grimes, Shulz, Van Vliet & Stanwood, 2007). Because of the possible increased risk of expulsion, the WHO classifies IUD insertion after an uncomplicated second-trimester abortion as category 2, which means the advantages of using the method generally outweigh the risks (WHO, 2009).

Quality of evidence

There is limited clinical data to support the recommendation of starting methods other than the IUD immediately after second-trimester D&E. This recommendation is based on expert opinion (WHO, 2009). A woman's

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immediate need for reliable contraception after abortion, coupled with the risk that delayed contraceptive provision reduces uptake, strongly supports the recommendation to start these methods immediately.

Young women

The IUD for women under the age of 20 is classified by WHO as category two, in which the benefits generally outweigh the risks. While risk is slightly increased due to higher rates of sexually transmitted infections and expulsion in this patient population, IUDs are still a safe, effective and recommended method for women under the age of 20. Sterilization may be performed, but a young woman will need special precautions due to the increased risk of regret (WHO, 2009).

References

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Second-trimester medical abortion and dilatation and evacuation (D&E): Follow-up

Recommendation:

Routine follow-up care is not necessary unless desired or requested by the woman or necessary for her chosen contraceptive method. She should receive adequate information regarding her postabortion care and warning signs prior to being sent home

Strength of recommendation: Weak

Quality of evidence: Very low

Last reviewed: June 5, 2013

Follow-up

There is no scientific data to demonstrate that routine follow-up is beneficial after second-trimester abortion performed by a trained health-care provider. In addition, there is no evidence to suggest that a pelvic examination is beneficial in an asymptomatic woman if she does return for a routine follow-up visit.

Young women

The recommendation for follow-up after second-trimester medical abortion or dilatation and evacuation (D&E) is the same for both young women and adults.

Quality of evidence:

Very low. The recommendation is based on expert opinion (WHO, 2012).

References

WHO. (2012). *Safe abortion: Technical and policy guidance for health systems* (2nd ed.). Geneva: World Health Organization.

Second-trimester dilatation and evacuation (D&E): Cervical preparation

Recommendation:

- Routine preoperative cervical preparation is recommended before dilatation and evacuation (D&E) (WHO, 2012).
- Osmotic dilators, misoprostol and mifepristone are all choices for cervical preparation. The choice depends on availability, expense, gestational age and timing of the procedure.

Strength of recommendation: Strong

Quality of evidence: High

Last reviewed: June 5, 2013

Background

Cervical preparation prior to second-trimester dilatation and evacuation (D&E) reduces the risk of complications (Fox & Hayes, 2007; Peterson, Berry, Grace, & Gulbranson, 1983). There is limited data to suggest the best method because the trials that exist have heterogeneous comparisons, small enrollment numbers and exclude women with pregnancies over 20 weeks. Although trials may show differences in cervical dilation, they are not large enough to show differences in more serious outcomes like cervical or uterine injuries or inability to complete the procedure (Newmann et al., 2010). Moreover, method choice is often limited by availability, especially in low-resource settings. Possible cervical preparation methods include:

Method	Dosing	Note
Osmotic dilators (laminaria or synthetic dilators)	6-24 hours prior to procedure	
Misoprostol	400mcg buccally or vaginally three hours prior to procedure	Limited data to support use over 18 to 20 weeks. May be combined with osmotic dilators over 19 weeks. May be repeated as needed.
Mifepristone	200mg orally 24-48 hours prior to procedure	No data to support use over 16 weeks.

Osmotic dilators

Numerous cohort studies have demonstrated that osmotic dilators are safe and effective and their use does not increase infectious morbidity (Bryman, Granberg, & Norström, 1988; Fox & Hayes, 2007; Jonasson, Larsson, Bygdeman, & Forsum, 1989; Peterson, et al., 1983). A Cochrane meta-analysis of cervical preparation before D&E showed that osmotic dilators provide better cervical dilation when compared to prostaglandins throughout the second trimester and decreased procedure time in the early second trimester. There is not sufficient evidence to

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recommend a specific dilator type (laminaria or synthetic dilators) or regimen (Newmann, Dalve-Endres, & Drey, 2008). Decisions about the number and timing of dilators to place should be individualized and take into consideration dilator's type and size, the woman's gestational age, parity and cervical compliance, and the provider's experience (Fox & Hayes, 2007; Newmann et al., 2008).

Misoprostol

Misoprostol has been studied as an alternative or supplement to osmotic dilators. One randomized controlled trial of 84 women up to 16 weeks showed that women who had 400mcg vaginal misoprostol three to four hours prior to the procedure had less cervical dilation and longer procedure times than women with overnight laminaria. However, all of the procedures could be completed and women preferred misoprostol to laminaria (Goldberg et al., 2005). In an observational study of 429 women in Vietnam between 13-18 weeks gestation, misoprostol alone was found to be adequate for cervical preparation but nine percent of women required repeat dosing (Castleman, Oanh, Hyman, Thuy, & Blumenthal, 2006). Repeat dosing of misoprostol was used to successfully complete same-day second-trimester D&E in one single-center case series of 1,081 women from 17 to 20 weeks (Maurer, Jacobson & Turok, 2013).

Case series have shown that adding misoprostol to laminaria for cervical preparation is effective but comparative data to support this practice is sparse (Lyus, Lohr, Taylor & Moroni, 2013; Nucatola, Roth, Saulsberry & Gatter, 2008). A randomized controlled trial of 125 women showed that 400mcg buccal misoprostol added to overnight laminaria improved cervical dilation when compared to laminaria alone in women over 19 weeks gestation. This effect was not seen at lower gestational ages (Edelman, Buckmaster, Goetsch, Nichols & Jensen, 2006). Although misoprostol might not produce as great a degree of cervical dilation, it is cheap, safe (Nucatola, Roth, Saulsberry & Gatter, 2008), and more readily available than osmotic dilators in some low-resource settings and appears to be a reasonable option as the main agent for cervical preparation prior to D&E up to 18 weeks gestation (Baird, Castleman, Hyman, Gringle & Blumenthal, 2007). Misoprostol may be given to women with a prior cesarean delivery, as uterine rupture is rare in this setting (Fox & Hayes, 2007).

Mifepristone

In a randomized trial of 50 women between 14-16 weeks gestation, women who had cervical preparation with osmotic dilators had a slightly shorter procedure time and greater dilation compared to mifepristone, but women had less pain with mifepristone and strongly preferred mifepristone to osmotic dilators (Borgatta et al., 2012). In one clinical trial of 900 women between 12-20 weeks gestation given mifepristone with misoprostol, the combined regimen improved dilation compared to misoprostol alone but had a high rate of pre-procedure fetal expulsions (Carbonell et al., 2007). Because of the risk of fetal expulsion, mifepristone and misoprostol is not recommended prior to D&E (Newmann et al., 2010).

Young women

This recommendation is the same for young women as for adult women.

References

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Second-trimester dilatation and evacuation (D&E): Pain management

Recommendation:

- Women undergoing second-trimester dilatation and evacuation (D&E) should receive pain medications and non-pharmacologic approaches to treat pain (WHO, 2012).
- A combination regimen of local anesthesia (paracervical block), non-steroidal anti-inflammatory drugs and narcotic analgesics with or without anxiolytics is recommended. If the personnel, monitoring and equipment are available to safely provide deeper levels of sedation, these services may be offered. The increased risks of deep sedation or general anesthesia must be weighed against the benefits to the woman.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: June 5, 2013

Pain during second-trimester dilatation and evacuation

There is a lack of published evidence regarding the level of pain associated with dilatation and evacuation (D&E). Most experts agree that D&E is more painful than first-trimester vacuum aspiration; D&E requires more dilation, longer procedure times and deeper uterine manipulation.

Regimens for pain control

Specific studies in second-trimester D&E are lacking. The optimal regimen for pain management has not been established. Most international consensus statements focus on the minimum amount of anesthesia at which a D&E can be performed to ensure access at lower-level facilities rather than optimizing pain control (RCOG, 2011; WHO, 2012). Ipas recommends a combination of local anesthesia (paracervical block) with NSAIDs and narcotic analgesics with or without anxiolytics. Medications may be given orally or parenterally (Baird, Castleman, Hyman, Gringle & Blumenthal, 2007).

Some women may need deeper sedation based on the clinical situation. Intravenous sedation may be offered in facilities where there is a trained provider with adequate equipment for patient monitoring. General anesthesia increases the risks associated with abortion and is not recommended for routine procedures (Atrash, Cheek, & Hogue, 1988; WHO, 2012). If general anesthesia is used, the addition of a paracervical block does not appear to help with postoperative pain control (Lazenby, Fogelson & Aeby, 2009). Medication choice and sedation level depend on the woman's preference as well as the level of provider training, supplies and monitoring equipment in the facility.

Young women

This recommendation is the same for young women as for adult women.

Clinical Updates in Reproductive Health

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Second-trimester dilatation and evacuation (D&E): Prophylactic antibiotics

Recommendation:

Administer prophylactic antibiotics for all women prior to dilatation and evacuation (D&E). Where antibiotics are unavailable, D&E may still be offered. Some providers start antibiotics at the time of osmotic dilator placement, but there are no studies comparing different start times and the risk of infection.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: June 6, 2013

Background

There is evidence to support the use of prophylactic antibiotics before first-trimester vacuum aspiration. However, evidence in the second trimester is more limited. Because of the demonstrated benefit of first-trimester antibiotics, the World Health Organization (WHO, 2012), Society of Family Planning (Achilles & Reeves, 2011), American Congress of Obstetricians and Gynecologists (ACOG, 2009) and Royal College of Obstetricians and Gynaecologists (RCOG, 2011) recommend prophylactic antibiotics for all women having dilatation and evacuation (D&E). Giving prophylactic antibiotics is more effective (Levallois & Rioux, 1988) and cheaper (Penney et al., 1998) than screening all women and treating only those with evidence of infection. Because the rate of infection after D&E is very low, the inability to provide antibiotics should not limit access to abortion (Peterson, Berry, Grace & Gulbranson, 1983; WHO, 2012).

Regimen

Many antibiotic regimens for abortion prophylaxis have been studied, but the ideal antibiotic, dose and timing has not yet been established (Achilles & Reeves, 2011). Tetracyclines (doxycycline) and nitroimidazoles (metronidazole and tinidazole) are commonly used because of their clinical efficacy, oral availability, low cost and low risk of allergic reactions (Achilles & Reeves, 2011; O'Connell, Jones, Lichtenberg, & Paul, 2008). Although studies of abortion are limited (Caruso et al., 2008) evidence from the obstetrical (Costantine et al., 2008), gynecologic (Mittendorf et al., 1993) and general surgery (Classen et al., 1992) literature supports the practice of giving antibiotics before the procedure to decrease the risk of infection. To reduce the incidence of nausea with pre-operative antibiotics, doxycycline may be given up to 10-12 hours before the procedure with a meal (Darj, Stralin, & Nilsson, 1987). Antibiotic regimens do not need to be extended beyond the immediate postabortion period (Achilles & Reeves, 2011; Levallois & Rioux, 1988; Caruso, et al., 2008; Lichtenberg & Shott, 2003).

The following table lists some common regimens used in clinical practice or recommended by professional organizations. These regimens are based on clinical evidence and expert opinion. Providers should choose a regimen based on the expense and availability of the antibiotics as well as practices around testing and treating women for sexually transmitted infections.

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Common Regimens	Recommender
Doxycycline 100mg orally one hour before the procedure and 200mg after the procedure <i>or</i> Metronidazole 500mg orally twice daily for five days	American Congress of Obstetricians and Gynecologists (ACOG, 2009)
Azithromycin 1g orally on the day of abortion, plus metronidazole 1g rectally or 800mg orally prior to or at the time of abortion <i>or</i> Doxycycline 100mg orally twice daily for seven days starting on the day of abortion, plus metronidazole 1g rectally or 800mg orally prior to or at the time of abortion <i>or</i> Metronidazole 1g rectally or 800mg orally prior to or at the time of abortion for women who have tested negative for <i>C. trachomatis</i> infection	Royal Congress of Obstetricians and Gynaecologists (RCOG, 2011)

Antibiotics with cervical preparation

Although not well studied, cervical preparation with osmotic dilators does not appear to increase the risk of infection (Fox & Hayes, 2007; Jonasson, Larsson, Bygdeman & Forsum, 1989). Some providers start antibiotics at the time of osmotic dilator placement, but there are no studies comparing different start times and the risk of infection (O'Connell, et al., 2008).

Young women

This recommendation is the same for young women as for adult women.

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Second-trimester medical abortion with mifepristone and misoprostol or misoprostol only: Previous uterine scar

Recommendation:

<22-24 weeks gestation with uterine scar

No regimen changes necessary. Please see *Clinical Updates in Reproductive Health* on “Second-trimester medical abortion with mifepristone and misoprostol: Recommended regimen” or “Second-trimester medical abortion with misoprostol only: Recommended regimen.”

>22-24 weeks gestation with one uterine scar or throughout second trimester with more than one uterine scar

Consider removing the misoprostol loading dose and decreasing the misoprostol dose with or without increasing the misoprostol dosing interval. There is insufficient evidence to suggest that these interventions will decrease the risk of uterine rupture in these women.

Strength of recommendation: Weak

Quality of evidence: Low

Last reviewed: June 17, 2013

Risk of uterine rupture with medical abortion

Uterine rupture has been reported during second-trimester medical abortion in women both with and without a uterine scar. The risk of uterine rupture for any woman undergoing a second-trimester medical abortion is very rare, occurring in less than 1/1,000 women (Goyal, 2009). In a meta-analysis of 16 studies of 3,556 women undergoing second-trimester medical abortion with combined or misoprostol-only regimens, there were three women who suffered uterine rupture resulting in a rate of 0.28 percent with a previous cesarean section and 0.04 percent without a previous cesarean section (Goyal, 2009).

One single-center retrospective review of 279 women undergoing second-trimester abortion with misoprostol every four hours included 26 women with more than one scar. These women received misoprostol 200mcg every four hours; three had a uterine rupture. (Küçükgöz Güleç et al., 2013).

Regimen for women with a uterine scar

Due to the rarity of uterine rupture in women with a previous scar, no clear guidance can be obtained from the published literature (Borgatta & Kapp, 2011; Daponte, Nzewenga, Dimopoulos & Guidozi, 2006; Daskalakis et al., 2004; Dickinson, 2005).

Expert opinion supports:

1. No change in medical abortion regimen for women whose gestation is less than 22-24 weeks.
2. After 22-24 weeks gestation with a single uterine scar or throughout the second trimester with more than one uterine scar:
 - a. No misoprostol loading dose.

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b. Consider decreasing the dose of misoprostol with or without increasing the dosing interval (Ho et al., 2007; Küçükgöz Güleç et al., 2013).

c. There is insufficient evidence to suggest that changing the dosing regimen will decrease the risk of uterine rupture.

Young women

This recommendation is the same for young women as for adult women.

References

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Second-trimester medical abortion: Pain management

Recommendation:

- All women undergoing medical abortion in the second trimester should be offered pain management (WHO, 2012).
- Prophylactic non-steroidal anti-inflammatory drugs reduce the need for narcotic analgesics during second-trimester medical abortion.
- All women should be given NSAIDs beginning with misoprostol. Narcotic analgesics, anxiolytics, and non-pharmacologic measures may be used as needed. If the personnel, monitoring and equipment are available, regional anesthesia or patient-controlled anesthesia may be offered.

Strength of recommendation: Strong

Quality of evidence: Low

Last reviewed: June 5, 2013

Pain during second-trimester medical abortion

In multiple cohort studies of second-trimester medical abortion, the majority of women require pain medication (Ashok, Templeton, Wagaarachchi & Flett, 2004; Gemzell-Danielsson & Östlund, 2000; Goh & Thong, 2006; Hamoda, Ashok, Flett & Templeton, 2004; Rose, Shand & Simmons, 2006). Advanced gestational age, number of misoprostol doses and induction-to-abortion interval are associated with increased pain during medical abortion (Hamoda, et al., 2004). Pain rarely starts after taking mifepristone but becomes more pronounced after misoprostol and typically peaks with expulsion.

Regimens for pain control

All women undergoing medical abortion in the second trimester should be offered pain management, but there is little evidence regarding the optimal regimen. One randomized trial of 74 women undergoing second-trimester medical abortion with mifepristone and misoprostol found that prophylactic treatment with a non-steroidal anti-inflammatory drug (diclofenac 100mg orally) at the time of misoprostol administration reduced the need for intravenous opiates when compared to treatment with paracetamol and codeine (Fiala, Swahn, Stephansson & Gemzell-Danielsson, 2005). In this study, treatment with NSAIDs did not affect abortion outcome.

In the largest cohort study of 1,002 women having second-trimester mifepristone and misoprostol medical abortion, a combination of oral and parenteral narcotic analgesics and nonsteroidal anti-inflammatory drugs was provided at four to six hour intervals as required (Ashok, et al., 2004). Although it is not evidence based, a combination regimen involving prophylactic NSAIDs given at the time of misoprostol, plus oral and/or parenteral narcotic analgesics, is an effective way of delivering pain management according to a woman's particular needs (Baird, Castleman, Hyman, Gringle, & Blumenthal, 2007). If the personnel, monitoring and equipment are available, regional (i.e. epidural) or patient-controlled anesthesia may be offered.

Young women

This recommendation is the same for young women as for adult women.

References

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Second-trimester medical abortion with mifepristone and misoprostol: Safety and efficacy

Summary of evidence:

A combined regimen with mifepristone and misoprostol is preferred for second-trimester medical abortion (WHO, 2012). The combined regimen is safe and effective, with expulsion rates of over 99 percent, induction-to-abortion time of around six hours and major complication rates of less than one percent.

Quality of evidence: High

Last reviewed: June 6, 2013

Expulsion rates

In the largest cohort study of 1,102 women having second-trimester medical abortion using the recommended mifepristone and misoprostol regimen, the complete expulsion rate was 98.3 percent at 24 hours and 99.2 percent at 36 hours (Ashok, Templeton, Wagaarachchi & Flett, 2004).

Induction-to-abortion interval

In the cohort study mentioned above, the median time to fetal expulsion was 6.25 hours, with a range of 0-67.5 hours. The induction-to-abortion interval was longer in nulliparous women, older women and women at a later gestational age (Ashok, et al., 2004). The addition of mifepristone to the medical abortion regimen consistently reduces the induction-to-abortion interval (Kapp, Borgatta, Stubblefield, Vragovic & Moreno, 2007; Ngoc et al., 2011).

Complication rates

The rate of major complications from mifepristone and misoprostol medical abortion in the second trimester is low, although minor complications such as needing a procedure for bleeding or retained products of conception are more frequent than for dilatation and evacuation (Autry, Hayes, Jacobson & Kirby, 2002). In the cohort of 1,002 women, 81 women (8.1 percent) needed surgery for uterine evacuation, the majority for retained placenta. Only two out of the 1,002 women needed a surgical evacuation to terminate the pregnancy (Ashok, et al., 2004). In this study, serious complications such as hemorrhage blood transfusion or unanticipated surgery occurred in eight women (<1 percent). In a meta-analysis of studies of medical abortion, the overall rate of uterine rupture is 0.08 percent, with a rate of 0.28 percent in women with a previous cesarean section (Goyal, 2009).

References

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Second-trimester medical abortion with mifepristone and misoprostol: Recommended regimen

Recommendation:

For women who are 13-24 weeks gestation:

Mifepristone 200mg by mouth, followed 36 to 48 hours later by misoprostol 800mcg vaginally for one dose, then 400mcg vaginally or sublingually every three hours for four more doses (WHO, 2012).

Strength of recommendation: Strong

Quality of evidence: Up to 20 weeks gestation, moderate. 20-24 weeks gestation, low.

Last reviewed: June 6, 2013

Background

Mifepristone combined with misoprostol is the preferred regimen for medical abortion in the second trimester as it combines high efficacy, a short induction-to-abortion interval and an excellent safety profile (Wildschut et al., 2011).

Mifepristone dose and timing

Mifepristone 200mg given orally is as effective as a 600mg dose (Webster, Penney, & Templeton, 1996). When mifepristone is given 24 hours instead of 48 hours before misoprostol, the induction-to-abortion interval is longer but the abortion rate at 24 hours is similar (Heikinheimo, Suhonen & Haukkamaa, 2000; Nilas, Glavind-Kristensen, Vejborg & Knudsen, 2007). Although it is less effective than waiting 36 to 48 hours, simultaneous dosing of mifepristone and misoprostol can be a useful strategy if medical or social issues require a shorter time interval between the two medications (Chai et al., 2009) as the combined regimen is still more effective than misoprostol alone.

Misoprostol loading dose

Published clinical trials have used a higher loading dose of vaginal misoprostol 600mcg (Chai, et al., 2009; el-Refaey & Templeton, 1995) or 800mcg (Hamoda, Ashok, Flett & Templeton, 2005); however, the high loading dose has never been directly compared to a standard dose protocol of 400mcg of misoprostol. The largest case series of 1,002 women undergoing mifepristone-misoprostol second-trimester abortion used a loading dose of misoprostol 800mcg vaginally with a resulting median induction-to-abortion interval of 6.25 hours and 24-hour efficacy of 97.1 percent (Ashok, Templeton, Wagaarachchi & Flett, 2004). When compared to the 800mcg vaginal loading dose, a 600mcg sublingual loading dose has similar efficacy but higher pain medication requirements (Hamoda, et al., 2005).

Misoprostol dosing

Route: Vaginal dosing has superior efficacy when compared to oral dosing (Wildschut, et al., 2011). Sublingual dosing has similar efficacy to vaginal, but it is associated with higher pain medication requirements (Hamoda, et al., 2005). Oral dosing is inferior to vaginal and sublingual dosing (Ho, Ngai, Liu, Wong, & Lee, 1997; Tang, Chan, Kan, & Ho, 2005). More research is needed to determine the most effective dose and timing for buccal

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misoprostol (Ellis, Kapp, Vragpvoc & Borgata, 2010).

Dose: Misoprostol 400mcg vaginally has higher expulsion rates, shorter induction-to-abortion intervals and similar side effects compared to 200mcg vaginally (Brouns, van Wely, Burger & van Wijngaarden, 2010). The 400mcg dose is equally effective when given sublingually (Hamoda, et al., 2005).

Timing: In studies of misoprostol only, induction-to-abortion intervals were shorter and efficacy at 24 hours was higher when misoprostol was given every three hours compared to every six hours with similar rates of adverse events (Wong, Ngai, Yeo, Tang & Ho, 2000).

Quality of evidence: The recommendation is based on multiple randomized clinical trials and a Cochrane meta-analysis comparing different mifepristone and misoprostol doses, dosing intervals and routes of administration in the second trimester (Wildschut, et al., 2011). Most randomized controlled trials of medical abortion in the second trimester do not include women over 20 week's gestation.

Young women

This recommendation is the same for young women as for adult women.

References

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Second-trimester medical abortion with misoprostol only: Safety and efficacy

Summary of evidence

A combined regimen with mifepristone and misoprostol is preferred for second-trimester medical abortion (WHO, 2012). Where mifepristone is not available, misoprostol only is safe and effective with expulsion rates of over 90 percent at 48 hours, average induction-to-abortion time of around 12 hours and major complication rates of less than one percent.

Quality of evidence: Moderate

Last reviewed: June 6, 2013

Expulsion rates

In the largest international randomized controlled trial of 681 women having second-trimester medical abortion using the recommended misoprostol-only regimen, the complete expulsion rate was 84.8 percent at 24 hours and 94.3 percent at 48 hours (Von Hertzen et al., 2009). Other randomized trials using vaginal or sublingual misoprostol every three hours show similar expulsion rates of 90 percent to 95 percent at 48 hours (Bhattacharjee, Saha, Ghoshroy, Bhowmik & Barui, 2008; Tang, Lau, Chan, & Ho, 2004). In nulliparous women, vaginal misoprostol has higher expulsion rates than sublingual misoprostol (Von Hertzen, et al., 2009).

Induction-to-abortion interval

In the trial cited above, the median time to fetal expulsion was 12 hours with a range of 4.1-61.8 hours, with parous women having faster induction-to-abortion times than nulliparous women (Von Hertzen, et al., 2009). Increasing the dosing interval of misoprostol increases the induction-to-abortion time (Wong, Ngai, Yeo, Tang, & Ho, 2000).

Complication rates

The rate of major complications from misoprostol-only abortion in the second trimester is low. In the trial cited above, 12 adverse events (0.02 percent) were reported, with none of them being serious (Von Hertzen, et al., 2009); ten women required blood transfusions.

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Second-trimester medical abortion with misoprostol only: Recommended regimen

Recommendation:

For women who are 13 to 24 weeks gestation:

Misoprostol 400mcg vaginally or sublingually every three hours for up to five doses. Vaginal dosing is more effective than sublingual dosing for nulliparous women (WHO, 2012).

Strength of recommendation: Strong

Quality of evidence: Up to 20 weeks gestation, moderate. 20-24 weeks gestation, low.

Last reviewed: May 22, 2013

Background

In the second trimester, a combination regimen with mifepristone and misoprostol has shorter induction-to-abortion intervals and higher success rates than misoprostol only (Wildschut et al., 2011). If mifepristone is not available, a misoprostol-only regimen with dosing every three hours is an acceptable alternative (Wildschut et al., 2011; WHO, 2012).

Vaginal route

In randomized controlled clinical trials, misoprostol 400mcg vaginally every three hours is associated with a median induction-to-abortion interval of 10-15 hours and a 48-hour successful abortion rate of 90 percent to 95 percent (Bhattacharjee, Saha, Ghoshroy, Bhowmik & Barui, 2008; Tang, Lau, Chan, & Ho, 2004; von Hertzen et al., 2009). Increasing the dosing interval decreases the efficacy of medical abortion (Wong, Ngai, Yeo, Tang & Ho, 2000).

Sublingual route

In a meta-analysis of 1,178 women from three randomized controlled trials, misoprostol 400mcg sublingually is similar (Bhattacharjee, et al., 2008) or slightly inferior to vaginal dosing when given every three hours (Tang, et al., 2004; von Hertzen, et al., 2009; Wildschut, et al., 2011). In the trials that showed reduced efficacy, the difference was driven by an inferior response to sublingual misoprostol in nulliparous women only. Of note, all of these studies found women prefer the sublingual route to the vaginal route.

Other routes

Buccal route: One randomized trial of 64 women showed buccal misoprostol was as effective as vaginal misoprostol. However, all of the women in this trial received a loading dose of misoprostol 400mcg vaginally and were randomized to 200mcg buccally or vaginally every six hours (Ellis, Kapp, Vragpvc & Borgata, 2010). More studies are needed before recommending buccal misoprostol for this purpose.

Oral route: In multiple randomized clinical trials, oral dosing has been shown to be less effective with longer induction-to-abortion intervals than vaginal dosing (Akoury et al., 2004; Bebbington et al., 2002; Behrashi & Mahdian, 2008).

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Quality of evidence: The recommendation is based on multiple randomized clinical trials and a Cochrane meta-analysis comparing different misoprostol doses, dosing intervals and routes of administration in the second trimester (Wildschut, et al., 2011). Most randomized controlled trials of medical abortion in the second trimester do not include women over 20 week's gestation.

Young women

This recommendation is the same for young women as for adult women.

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Misoprostol for treatment of incomplete and missed abortion (postabortion care) under 13 weeks uterine size: Recommended regimen

Recommendation:

Incomplete Abortion: Misoprostol 600mcg orally in a single dose or 400mcg sublingually in a single dose (WHO, 2012).

Missed abortion: Misoprostol 800mcg vaginally in a single dose or 600mcg sublingually every three hours for a maximum of three doses (1,800mcg).

Strength of recommendation: Strong

Quality of evidence: Moderate

Last reviewed: May 21, 2013

Definitions

Incomplete abortion: An abortion—whether spontaneous or induced—in which some pregnancy tissue passes out of the uterus but some remains.

Missed abortion: A kind of miscarriage; the pregnancy ends, but the tissue remains in the uterus.

Incomplete abortion

In nine studies of 1,499 women presenting with incomplete abortion under 13 weeks, management with misoprostol shows similar success to surgical management in achieving complete abortion (Neilson, Gyte, Hickey, Vazquez, & Dou, 2010). Misoprostol 600mcg taken orally as a single dose has a 91- to 99-percent complete abortion rate (Bique et al., 2007; Dao et al., 2007; Montesinos et al., 2011; Shwekerela et al., 2007; Weeks et al., 2005). Misoprostol 400mcg taken sublingually as a single dose has similar efficacy (Blandine et al., 2012; Dabash et al., 2011; Diop et al., 2009). Lengthening the time to follow-up increases the success of misoprostol treatment.

Missed abortion

A single dose of misoprostol 800mcg vaginally results in successful uterine evacuation in more than 80 percent of women (Demetroulis, Saridogan, Kunde, & Naftalin, 2001; Ngoc, Blum, Westheimer, Quan, & Winikoff, 2004). Some studies have used repeat doses of misoprostol 800mcg vaginally after 24 (Graziosi, Mol, Ankum, & Bruinse 2004; Muffley, Stitely, & Gherman, 2002) or 72 (Gilles et al., 2004; Zhang et al., 2005) hours with a resulting increase in the complete abortion rates. However, it is unclear whether the increase in complete abortion is due to the additional prostaglandin dose or the increased time to evaluation. When women are managed expectantly after a single dose of misoprostol, their complete abortion rates increase over time (Ngoc et al., 2004). Misoprostol 600mcg sublingually repeated every three hours for a maximum of two more doses achieves similar success rates (Tang, Ong, Tse, Ng, Lee, & Ho, 2003; Tang et al., 2006).

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Young women

The treatment of incomplete and missed abortion is the same in young women as in adult women, however in a secondary analysis of 485 misoprostol users (Creinin et al., 2006) nulliparity was associated with twice the likelihood of successful treatment with a single dose of misoprostol (800mcg vaginally).

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Vacuum aspiration for treatment of incomplete and missed abortion (postabortion care): Prophylactic antibiotics

Recommendation:

Routine prophylactic antibiotics are recommended for treatment of incomplete or missed abortion with vacuum aspiration (commonly referred to as postabortion care). Where antibiotics are unavailable, uterine aspiration may still be offered. Women with signs or symptoms of infection should be given therapeutic antibiotics.

Strength of recommendation: Weak

Quality of evidence: Very low

Last reviewed: June 5, 2013

Background

Scant literature supports the use of routine antibiotics during vacuum aspiration for incomplete or missed abortion (commonly referred to as postabortion care) (May, Gülmezoglu, & Ba-Thike, 2007). However, routine prophylactic antibiotics are recommended before vacuum aspiration for induced abortion (WHO, 2012), and therefore in the absence of evidence, it seems prudent to administer prophylactic antibiotics for vacuum aspiration when used for postabortion care (Achilles & Reeves, 2011). The inability to provide antibiotics should not limit access to vacuum aspiration (WHO, 2012), as the overall risk of infection is low.

Regimen

Many antibiotic regimens for abortion prophylaxis have been studied, but the ideal antibiotic, dose and timing has not yet been established (Achilles & Reeves, 2011). Tetracyclines (doxycycline) and nitroimidazoles (metronidazole and tinidazole) are commonly used because of their clinical efficacy, oral availability, low cost and low risk of allergic reactions (Achilles & Reeves, 2011). A short pre-operative course of oral doxycycline or metronidazole may be used in clinical practice.

Therapeutic antibiotics

Women who present with signs and symptoms of infection should be treated with broad spectrum oral or intravenous antibiotics according to the severity of the infection.

Quality of evidence

A Cochrane review of antibiotics for incomplete abortion found only one randomized controlled trial from Zimbabwe with 140 women that showed no benefit from a course of oral tetracycline after uterine evacuation (May, Gülmezoglu, & Ba-Thike, 2007; Seeras, 1989). United States trials of prophylactic oral (Ramin et al., 1995) or intravenous doxycycline (Prieto, Eriksen & Blanco, 1995) and a Thai trial of intramuscular cefoxitin (Titipant & Cherdchoogiat, 2012) before evacuation for incomplete abortion have shown no reduction in postoperative infection with antibiotics.

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Young women

This recommendation is the same for young women as for adult women.

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Pain medication table

Though the medications shown below are commonly used for pain management during vacuum aspiration and dilatation and evacuation, many other options exist. This table does not cover general anesthetic agents.

Both anxiolytics and narcotics may cause respiratory depression, especially when they are used together. Accordingly, lower doses should be used when they are together than when they are separate. When medications are given intravenously immediately before a procedure they should be given slowly and intermittently by a specially trained provider. Problematic side effects can be avoided by repeated small intravenous doses that are titrated to a woman’s level of pain and sedation. The peak analgesic effect should occur during the procedure to avoid excessive post procedure sedation.

Even clinicians using lighter sedation analgesia must be able to manage respiratory arrest, in the unlikely event that an unintentional overdose should occur. Providers should be trained in airway management and cardiopulmonary resuscitation, and resuscitative equipment and appropriate antagonist drugs (naloxone and flumazenil) should be available.

** Disclaimer: This resource is designed to be a supplemental resource for clinicians and is NOT intended to serve as a replacement for drug label information or clinical judgment that accounts for patients' and facilities' unique circumstances.*

Last reviewed: May 30, 2013

Drug type	Generic drug name	Dose and timing	Half-life	Side effects	Comments
Local anesthetic	Xylocaine	15-20ml of 0.5%-1% solution in a paracervical block not to exceed 4.5mg/kg	60-90 minutes	Buzzing in ears; dizziness; numbness in lips, mouth and tongue; metallic taste; seizures (rare)	<p>Pull back plunger before injecting to avoid intravascular injection. Wait three minutes for medication to take effect.</p> <p>Mild reaction (itching, rash, and hives) can be treated with 25-50mg diphenhydramine IM or IV.</p> <p>For intense reaction or respiratory distress, obtain IV access immediately. Give epinephrine 0.4mg subcutaneously and diazepam 5mg slow IV push. Support</p>

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					<p>respiration. If wheezing is present, inhaler may be helpful.</p> <p>Allergic reaction is very rare. Reactions that do occur may be due to preservatives in multi-dose vials. Preservative-free lidocaine allergy is extremely rare.</p>
NSAID	Ibuprofen	Oral: 400-800mg one hour before the procedure	4-6 hours	Possible gastrointestinal upset	Do not use in women with active peptic ulcer disease or renal failure.
	Naproxen	Oral: 550mg one hour before the procedure	4-6 hours	Possible gastrointestinal upset	Do not use in women with active peptic ulcer disease or renal failure.
	Ketorolac	<p>Oral: 20mg one hour before procedure</p> <p>IV: 30mg over at least 15 seconds 30-60 minutes before procedure</p> <p>IM: 60mg 30-60 minutes before procedure</p> <p>For women less than 50kg, all doses should be halved</p>	4-6 hours		<p>Single dose IM ketorolac prior to surgery may reduce opioid use and postoperative pain (de Oliveira, 2012; Roche, 2011).</p> <p>Do not use in women with active peptic ulcer disease, renal failure, breastfeeding or sensitivity to other NSAIDs.</p> <p>Breakthrough pain should be managed with narcotics rather than increasing ketorolac beyond the recommended doses.</p>
Analgesic	Acetaminophen	Oral: 500-1,000mg 30-60 minutes before procedure	3-6 hours		<p>Not a first-line pain medication for vacuum aspiration or medical abortion. May be used as an antipyretic.</p> <p>Liver toxicity from overdose (maximum dose = 4,000mg/day) is a risk.</p>

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Narcotic/analgesic combination	Acetaminophen 300mg + codeine 30mg	Oral: 1-2 tablets one hour before procedure	3-6 hours	Drowsiness, light-headedness, nausea and vomiting, decreased breathing rate, loss of consciousness	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with naloxone (see below). Be aware of combining with other acetaminophen containing products. Liver toxicity from overdose of acetaminophen (maximum dose = 4,000 mg/day) is a risk.
	Acetaminophen 500mg + hydrocodone 5mg	Oral: 1-2 tablets one hour before procedure	4-6 hours	Drowsiness, light-headedness, nausea and vomiting, decreased breathing rate, loss of consciousness	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with naloxone (see below). Be aware of combining with other acetaminophen containing products. Liver toxicity from overdose of acetaminophen (maximum dose = 4,000 mg/day) is a risk.
Narcotic	Meperidine	Oral: 100-150mg 30-60 minutes before procedure IV: 25-50mg 5-15 minutes prior to procedure IM/SC: 50-100mg 30-90 minutes prior to procedure	4-6 hours	Drowsiness, light-headedness, nausea and vomiting, decreased breathing rate, loss of consciousness,, hypotension, seizures	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with naloxone (see below). More rapid onset and shorter duration of action than morphine. Meperidine 60-80mg = morphine 10mg.
	Fentanyl	IV: 50-100mcg immediately before procedure (may repeat every 10-15 minutes, not	30-60 minutes	Drowsiness, light-headedness, weakness, bradycardia, decreased breathing rate, loss of	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with naloxone



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		to exceed 250mcg) IM: 50-100mcg 30-60 minutes before procedure		consciousness,, hypotension, seizures	(see below). More rapid onset and shorter duration of action than meperidine. Fentanyl 100mcg = meperidine 75mg = morphine 10mg. Onset of action is 2-7 minutes when given IV.
	Tramadol	IV/IM: 50-100mg 15-30 minutes before the procedure Oral/suppository: 50-100mg 60-90 minutes prior to the procedure	4-6 hours	Drowsiness, light-headedness, sweating, weakness, fatigue, seizures	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with diazepam. Less respiratory depression than morphine or meperidine Tramadol 100mcg = morphine 10mg
Anxiolytic (Benzodiazepine)	Diazepam	Oral: 10mg one hour before procedure IV: 2-5mg IV 20 minutes before procedure	21-37 hours	Blurred vision, dizziness, disorientation, pain and redness on injection, decreased breathing rate, loss of consciousness	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with flumazenil (see below). Has a mild amnestic effect. Onset of action is 2-10 minutes when given IV.

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	Midazolam	IV: 1-2mg immediately before the procedure, then 0.5-1mg IV every five minutes as needed, not to exceed 5mg IM: 0.07-0.08mg/kg or about 5mg up to one hour before procedure	1-4 hours	Blurred vision, dizziness, disorientation, CNS and respiratory depression	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with flumazenil (see below). Midazolam 2.5mg = diazepam 10mg. Stronger amnestic effect than diazepam. Onset of action is 1-5 minutes when given IV and 15-30 minutes when given IM.
	Lorazepam	Oral: 1-2mg 30-60 minutes before procedure IV: 2mg given over one minute before the procedure IM: 0.05mg/kg up to a maximum of 4mg within two hours before the procedure	14 hours	Blurred vision, dizziness, disorientation, decreased breathing rate, loss of consciousness	If respiration is compromised, assist with breathing (airway management, oxygen and ambu bag) and reverse with flumazenil (see below). Amnestic effect. Occasionally may increase patient anxiety.
Reversal agent for narcotic	Naloxone	IV: 0.4mg vial mixed in 10mL saline. Give 1mL (40mcg/mL) every two minutes until reversal is seen			Naloxone's duration of action is one hour and may wear off before the narcotic. Therefore, patients treated with naloxone must be monitored closely for several hours. Maintain airway and respirations while

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<p>Reversal agent for benzodiazepine</p>	<p>Flumazenil</p>	<p>IV: 0.2mg every minute until respirations return. Do not exceed 1mg</p>		<p>giving naloxone.</p> <p>Flumazenil's duration of action is one hour and may wear off before the benzodiazepine. Therefore, patients treated with flumazenil must be monitored closely for several hours. In the event of overdose with narcotic and benzodiazepine, reverse the narcotic first with naloxone and use flumazenil subsequently if needed.</p> <p>Maintain airway and respirations while giving flumazenil.</p>
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