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Outlook

Misoprostol use in obstetrics and gynecology

Reducing maternal mortality is an essential health objective in much of the developing world. The United Nations' fifth Millennium Development Goal focuses on reducing maternal mortality ratios by three quarters by the year 2015. In many low-resource settings, however, the interventions recommended for reducing these ratios are neither available nor affordable. In these settings, increasing access to misoprostol—a synthetic prostaglandin E_1 analog that is used for a range of obstetric and gynecologic indications—could play an important role.

In 1988, the US Food and Drug Administration approved misoprostol under the brand name Cytotec® for prevention of gastric ulcers among long-term users of nonsteroidal anti-inflammatory drugs. Because misoprostol affects the uterus as well as the gastrointestinal tract, the US manufacturer warns against use of the drug by pregnant women.[1]

Since learning of the drug's effects, investigators around the world have shown a strong interest in understanding misoprostol's potential role for obstetric and gynecologic uses.[2] Misoprostol has been established as an effective adjunct to medical abortion regimens using mifepristone, and research into its effectiveness and limitations when used alone for medical abortion is ongoing. Equally important, researchers are assessing the use of misoprostol for other obstetric and gynecologic uses such as cervical ripening, induction of labor, prevention and treatment of postpartum hemorrhage, and postabortion care. While misoprostol is not approved for these indications in most countries, it is commonly used in obstetrics and gynecology.[3,4]

The purpose of this *Outlook* issue is to provide accurate, evidence-based information on the emerging use of misoprostol in obstetrics and gynecology. It should not be interpreted as recommending or supporting off-label use of misoprostol.

In this issue

PATH

Background

Since the late 1980s, hundreds of studies have supported the use of misoprostol for various obstetric and gynecologic indications (see Table 1).[3–5] Many have focused on misoprostol's potential role in areas that lack access to approved interventions.

Benefits for low-resource settings

Many uterotonic drugs traditionally used to induce labor or prevent or manage postpartum hemorrhage—such as oxytocin or other prostaglandins—can only be stored at room temperature for a few months or need to be refrigerated. They also often require injection. In contrast, misoprostol tablets produced under high-quality manufacturing conditions have a shelf life of several years if they are kept at room temperature and remain in their aluminum blister packets (which prevent contact with air). This characteristic could facilitate use in low-resource settings.

With an average wholesale cost of US$1.20 to $1.46 per 200-mcg tablet in the United States[6] and $0.33 to $0.55 in some developing countries,[7,8] misoprostol is less expensive than other uterotonic drugs for certain applications. A Ugandan study of induction of labor in women with intrauterine fetal death found that the average cost of treatment with vaginal misoprostol was $0.65, compared with $7.86 for intravenous oxytocin.[9] For prevention of postpartum hemorrhage, however, 10 IU of oxytocin and a disposable syringe are often available for less than $0.20, which is less than the cost of a comparable misoprostol regimen.

Table 1. State of current research on misoprostol

Indications for which there is well-established evidence	Indications for which there is good evidence*	Indications for which there is anecdotal evidence
• First- and second-trimester pregnancy termination in conjunction with mifepristone or methotrexate. • Cervical ripening before surgical pregnancy termination during the first trimester. • Labor induction with a viable fetus.	• First- and second-trimester pregnancy termination with misoprostol alone. • Management of spontaneous and incomplete abortion. • Labor induction for intrauterine fetal death. • Prevention and treatment of postpartum hemorrhage. • Cervical ripening before hysteroscopy and other gynecological procedures that require entry into the uterus.	• Cervical ripening before second- and third-trimester dilation and evacuation. • Cervical softening for IUD insertion, endometrial biopsy, or intrauterine insemination.

*Including at least one published, randomized, controlled trial. Source: Adapted from Shannon and Winikoff 2004.[4]

Regulatory issues

Cytotec is the most widely registered misoprostol brand. Cytotec was marketed by GD Searle & Company from 1988 to 2000 and is currently marketed by Pfizer Inc. Other brand names include Cityl (Colombia), Cyprostol (Austria), Cytolog (India), Gastotec (Korea), Gastrul (Indonesia), Gymiso (France), Misel (Korea), Misoprost (India), Prostokos (Brazil), U-Miso (Taiwan), Vagiprost (Egypt), and Zitotec (India).

In the United States, Cytotec is approved for one indication: reducing the risk of gastric ulcers caused by chronic use of nonsteroidal anti-inflammatory drugs. In most countries, misoprostol is not approved for obstetric or gynecologic indications. The notable exceptions are Brazil, Egypt, and France. In Brazil, Prostokos® is approved for induction of labor with a live fetus, uterine evacuation after fetal death, and legal termination of pregnancy. Prostokos is available as a 25-mcg formulation that is sold to hospitals; 100-mcg and 200-mcg formulations were approved in 2004 and are expected to be available to hospitals soon.[10,11] In Egypt, Vagiprost® is approved in a 25-mcg formulation for induction of labor.[12] In France, Gymiso® is approved in a 200-mcg formulation for medical termination of early pregnancy (less than 49 days amenorrhea) in combination with mifepristone.

In countries where misoprostol is approved only for prevention of gastric ulcers, use for obstetric or gynecologic purposes is "off-label" (see box, page 4).

Availability

Although availability varies according to supply logistics, prescribing practices, and regulatory issues, misoprostol is registered in more than 80 countries (see Figure 1, page 5). Most countries in the Americas and Asia have access to the drug, but many countries in Africa do not.

Access to misoprostol may be restricted based on its perceived uses. In Brazil, for example, the ministry of health tightened regulations to restrict misoprostol's use as an abortifacient. Several states enacted additional restrictions; in Ceara state, officials issued a complete ban.[13] In Thailand, officials restricted access to misoprostol in 2000 due to concerns about its use as an abortifacient among adolescents.[14]

Administration

Cytotec tablets are formulated for oral use. Studies of misoprostol regimens for obstetric and gynecologic uses have tested oral, vaginal, sublingual, buccal, and rectal routes of administration. The most effective administration route may depend on the indication for which the misoprostol tablets are used.

Both vaginal and oral administration appear effective for treatment of incomplete abortion.[15] With either route, multiple doses may be required. Vaginal administration generally allows more time between doses[16] and appears more effective for cervical ripening and induction of abortion than oral administration.[17,18] When assessing vaginal administration, researchers have investigated the effects of moistening the tablets with tap water or saline solution prior to insertion. Studies have found that moistening the tablets results in higher plasma levels compared with the same dose administered without water,[19] but the moistening has not been shown to have a significant effect on clinical outcomes.[20]

Sublingual administration, in which the tablets are placed under the tongue, holds promise for indications such as cervical ripening and medical abortion in the first trimester.[19,21,22] Buccal administration, in which the tablets are placed in the buccal (cheek) pouch, has been shown to be effective for cervical ripening and as part of mifepristone abortion regimens, but studies of buccal administration for cervical ripening show a higher incidence of side effects (e.g., tachycardia, which is an abnormally rapid heart rate) than

with vaginal administration.[23] In studies of misoprostol for treatment of postpartum hemorrhage, rectal administration has been shown to be effective.[24,25]

Dosage

As gestation advances, the uterus is increasingly sensitive to uterotonic agents. Misoprostol dosages therefore vary according to gestation as well as indication. Depending on the application, doses may consist of several misoprostol tablets and may need to be repeated over time.

Use during labor and delivery

Misoprostol is effective for inducing labor and is commonly used for this purpose in industrialized countries. Its effectiveness for preventing or treating postpartum hemorrhage is less clear.

Induction of labor

Several studies have shown that low doses—for example, 25 mcg—of vaginally administered misoprostol are more effective for inducing labor than oxytocin or dinoprostone.[26–29] While a 2002 meta-analysis found that, compared to 25-mcg doses, 50-mcg doses of misoprostol administered vaginally were associated with a shorter interval to vaginal delivery, greater proportion of deliveries within 24 hours, and less frequent need for oxytocin augmentation, the higher dose was associated with greater frequency of tachycardia and hyperstimulation syndrome.[30] Separation of cesarean scar and uterine rupture have been reported after misoprostol administration for induction of labor. (See "Safety" on page 5.)

Prevention and treatment of postpartum hemorrhage

Postpartum hemorrhage accounts for up to 25% of maternal mortality in some parts of the world.[31] Studies have demonstrated the effectiveness of oral and rectal misoprostol regimens for the prevention[32] and treatment[24] of postpartum hemorrhage. Unlike products such as Syntometrine® (a combination of oxytocin and ergometrine), which is routinely used to prevent postpartum hemorrhage in the industrialized world, misoprostol is not contraindicated in women with hypertension.[32]

In the largest study of misoprostol for prevention of postpartum hemorrhage to date, researchers found that, of more than 18,000 women who were randomized to two treatment groups, 4% of those who received 600 mcg of misoprostol immediately after delivery had a measured blood loss of 1,000 mL or more, compared with 3% of those who received 10 IU of oxytocin.[33] These results indicate that use of oxytocin is preferable to misoprostol for prevention of postpartum hemorrhage and could save a substantially greater number of women's lives. Some researchers have noted, however, that misoprostol is an important back-up option in settings where oxytocin is not available or where adequate storage conditions and safe-injection practices cannot be ensured.[34,35]

In Indonesia, researchers evaluated community-based distribution and use of misoprostol. Following one-on-one counseling during which pregnant women were instructed to take 600 mcg of misoprostol orally after childbirth, 999 women took the drug to prevent postpartum hemorrhage. Doctors or midwives attended only 40% of the births, so many women delivered without help and took misoprostol in a self-directed manner. Compared with women in a control area who did not have access to misoprostol, a smaller percentage of women in the intervention area perceived excessive bleeding after birth or needed an emergency referral for postpartum hemorrhage, but the differences were not statistically significant.[8]

Limited data are available on the use of misoprostol for treatment of postpartum hemorrhage. In a study of 14 women with postpartum hemorrhage that was unresponsive to oxytocin or ergometrine, researchers found that 1,000 mcg of rectally administered misoprostol controlled the hemorrhage and produced sustained uterine contraction within 3 minutes.[24] Additional research on misoprostol's effectiveness for this indication is needed.

Inducing or managing abortion

Health care providers use misoprostol to manage incomplete abortion, dilate the cervix before surgical abortion, and induce first- and second-trimester abortion. In addition, some women

What are uterotonic drugs?

Utertonic drugs are substances that cause the uterus to contract. They are especially helpful for inducing or augmenting labor, decreasing blood loss after delivery, and stimulating uterine contractility to induce abortion in the first or second trimesters.

The most commonly used uterotonic drug is a synthetic form of the naturally occurring hormone oxytocin. Oxytocin can be found in products such as Pitocin® and Syntocinon®. Oxytocic drugs induce contractions of smooth muscles of the uterus, hastening delivery or slowing blood loss after delivery.

Ergot-based compounds, another class of uterotonic drugs, are used only for controlling postpartum hemorrhage and helping the uterus return to its normal size after childbirth. Methergine® is the ergot preparation used today.

Prostaglandins, which also have uterotonic properties, are naturally occurring fatty acids found in the uterus, menstrual fluids, and amniotic fluids. Prostaglandins have a local effect and are metabolized quickly. Prostaglandins used for women's health include E_1 analogs such as misoprostol and gemeprost, E_2 analogs such as dinoprostone, and F_2-alpha analogs such as dinoprost and carboprost. Prostaglandins may be used as part of medical abortion regimens with mifepristone and to ripen the cervix.[36]

Off-label use of drugs

Regulatory approval of new drugs involves significant financial costs, years of clinical research, and efforts to minimize product liabilities. Therefore, manufacturers usually focus their research and development efforts on one potential use of a drug. Once a drug has been found safe and effective and is registered for one indication, informed clinicians may use the drug for additional indications. This use of an approved drug for other indications is referred to as "off-label use."

Off-label use of drugs is common. As the US Food and Drug Administration explains, "Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."[37]

have used misoprostol to self-induce abortions on their own.

Use of misoprostol for these indications appears to be acceptable to women. In a study of treatment for incomplete abortion, approximately 90% of women who received misoprostol viewed the side effects as tolerable.[38] In a study of 720 women who received misoprostol to induce early abortion, 74% had a "very good opinion" of the method, 21% had a "good opinion," and 2% had "no opinion."[39]

Treatment of incomplete abortion

Misoprostol regimens can be used to induce—and in some cases complete—the evacuation of retained products of conception in women with incomplete abortion. Some studies have shown that vaginal administration is more effective than oral administration for treatment of spontaneous abortion,[18,40] while others have found that both oral and vaginal regimens are effective.[41] In a Vietnamese study of 200 women with missed abortion (that is, asymptomatic, nonviable pregnancies), 89% of women who received misoprostol orally and 92% of women who received misoprostol vaginally did not need surgical intervention, but this difference was not statistically significant. Mean time to expulsion was significantly shorter among women who received misoprostol vaginally.[15]

In a randomized trial of women experiencing spontaneous abortion in Hong Kong, researchers compared misoprostol use with expectant management (that is, monitoring women without treatment to determine whether the abortion would be completed). After 5 days, women who had received 400 mcg of misoprostol vaginally on days 1, 3, and 5 showed a significantly higher rate of complete abortion than women in the expectant group (83.3% versus 48.3%, respectively).[20] In Thailand, a randomized study evaluated either one or two 600-mcg doses of misoprostol among women with incomplete abortion. Misoprostol treatment resulted in complete abortion in approximately 66% and 70% of the women, respectively.[38]

Preabortion cervical ripening

Mechanical dilation of the cervix prior to surgical abortion can lead to complications such as uterine perforation and cervical laceration.[42] Misoprostol regimens of 400 mcg administered vaginally 3 hours prior to uterine evacuation are effective for cervical ripening, resulting in dilation of at least 8 millimeters prior to first-trimester abortion.[43,44] Oral regimens of 200 to 400 mcg also have been shown to be effective and acceptable to women.[45,46] Research has shown that sublingual administration of 400 mcg of misoprostol may be more effective than the vaginal regimen, although sublingual administration is associated with a higher incidence of shivering[47] and appears less acceptable to women.[48]

Pregnancy termination

Misoprostol's effectiveness as an adjunct to mifepristone for medical abortion has been well established.[14] Where the recommended mifepristone-misoprostol regimen is not available, misoprostol-only regimens are being used to induce abortion in formal and informal health care settings. These regimens are less effective than the mifepristone regimen.[49]

Studies of misoprostol-only regimens have differed significantly in their designs, populations, administration routes, and dosages.[5] Many have shown high efficacy rates during the first trimester. For example, studies of 800-mcg doses administered vaginally have demonstrated complete-abortion rates greater than 85%.[39,49,50]

In 2003, Gynuity Health Projects and Reproductive Health Technologies Project convened professionals with epidemiological, clinical, and programmatic expertise who reached consensus on the most effective misoprostol regimen for abortion induction in pregnancies of up to 9 weeks: an 800-mcg dose of vaginal misoprostol, followed by a second 800-mcg dose after 24 hours.[51] While this consensus statement marks an important step toward a standardized regimen, randomized controlled trials are needed to define optimal dosing intervals, administration routes, and doses. Preliminary results from a World Health Organization (WHO) trial involving more than 2,000 women, for example, show that 3-hour dosing intervals are significantly more effective than 12-hour intervals, and that vaginal administration is more effective than sublingual administration.[40] These analyses are ongoing.

While misoprostol can be used to induce second-trimester abortion, it takes longer to have an effect, is less likely to result in complete abortion, and is associated with a higher

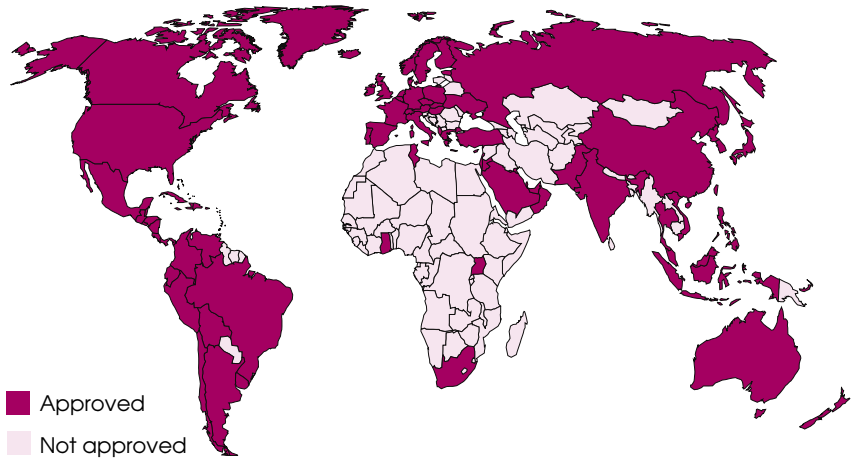
incidence of serious adverse events than first-trimester abortions.[40] Although limited in number, studies of misoprostol regimens used during the second trimester have demonstrated high rates of induced abortion with doses of 200, 400, 600, and 800 mcg that are repeated one or more times.[52–55] It is important to note that it may be necessary to surgically or manually remove the placenta after a second-trimester abortion; women also may experience heavy bleeding. For these reasons, all second-trimester abortions should be conducted in a hospital.[40]

Studies have shown that knowledge of misoprostol's abortifacient effects is high in some communities. In the Dominican Republic, investigators found that two-thirds of women interviewed in the street had heard of misoprostol and were aware that it could cause abortion. The investigators also found that the introduction of misoprostol coincided with a statistically significant decrease in life-threatening abortion complications among abortion admissions.[56] Similarly, results of a survey conducted in Southeast Asia, Africa, and Latin America indicate that women in some areas commonly self-administer misoprostol to terminate their pregnancies using varying doses and regimens.[57] Researchers in Brazil have noted similar trends (see box, page 6).

Postabortion care

Laws restrict, to varying degrees, the indications for legal abortion and the use of medications or procedures intended to induce abortion. Increasingly, however, ministries of health, professional associations, and other groups are emphasizing women's access to services for the management of complications arising from abortion—a priority outlined by the International Conference on Population and Development.[58] In many settings, women seek and receive postabortion care from hospital staff following the onset of bleeding after misoprostol administration. This has been well documented in Brazil.[13]

Figure 1. Countries where misoprostol is approved (2004)



Source: © Gynuity Health Projects 2004.[59]

Safety

Obstetric and gynecologic use of misoprostol may be most common where recommended uterotonics or prostaglandins are not available or affordable. Discussions of misoprostol safety in low-resource settings therefore should compare misoprostol to recommended drugs as well as to no treatment or to clandestine approaches. For example, in the case of induced abortion, misoprostol use can be compared to medically supervised use of abortifacients as well as the range of unsafe or ineffective methods that women may use[60]—such as herbal potions, insertion of foreign objects, or voluntary trauma.

Side effects and complications

The most common side effects associated with misoprostol use are nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever. These effects appear to be dose dependent. When used to induce first-trimester abortion, common symptoms—including bleeding, cramping, and nausea—are similar to those experienced during miscarriage.[3] After administration for second-trimester abortion, heavy bleeding has been reported.[40]

Severe complications resulting from misoprostol treatment are rare but serious. After misoprostol administration during the third trimester, both uterine rupture and separation of cesarean scar have been reported.[61] Although these reports are anecdotal, the frequency of uterine rupture after misoprostol administration appears much higher than after oxytocin administration.[62] No statistically significant effects on perinatal outcomes have been shown, but the possibility of serious adverse effects cannot be excluded.[26] Low doses and close clinical observation are recommended, and additional evaluations of misoprostol use for induction of labor are needed.[63]

Association with birth defects

Because abortion is legally restricted in many countries, women who attempt to induce abortion with misoprostol may have to carry their pregnancies to term if the attempt fails. Researchers in Brazil estimated that, in the early 1990s, misoprostol use occurred in 2.2% of pregnancies. This use was strongly associated with an unplanned pregnancy, absence of a husband or partner, and a history of previous induced abortion.[64]

Although the association may not be causative, misoprostol exposure *in utero* is associated with birth defects including equinovarus (clubfoot), cranial nerve anomalies, and absence of fingers. These defects may be caused by a temporary disruption in the blood

Women's use of misoprostol: the experience in Brazil

While women's use of misoprostol to self-induce abortion has been reported in numerous countries, the majority of published reports describe the experiences in Brazil. Abortion is illegal in Brazil except in cases of life-threatening complications or rape.

Shortly after Cytotec was approved for ulcer treatment in Brazil, use among women who wanted to self-induce an abortion became widespread. In the late 1980s, researchers estimated that, in the São Paulo area, at least 50% of all abortions were induced by Cytotec. Information about misoprostol administration and risks appears to have been exchanged informally among women and, in some cases, between women and pharmacists; no formal sources of information were available. Women reported using a range of doses and administration routes; simultaneously administering misoprostol by oral and vaginal routes was often described.

In 1991, as knowledge of this approach to self-induced abortions grew, Cytotec sales were severely restricted nationally and completely banned in Ceara state. Along with increasing anti-use campaigns in the media, these restrictions led to a marked drop in Cytotec sales in 1992. Researchers have noted that the attention placed on misoprostol by the media, clinicians, and women fueled awareness of the drug's abortifacient potential. At the same time, the debate may have helped create a more favorable environment for discussing abortion and possible legal reforms. Researchers observed that women who reported using misoprostol had a lower incidence of infection than women who stated that their abortions were not induced or had been induced by other methods. Among gynecologists, it was rumored that the number of septic abortion complications was dramatically lower after misoprostol became a popular method of illegally inducing abortion.[13,65–68]

Currently, misoprostol is available to hospitals in Brazil as a 25-mcg vaginal suppository (Prostokos).

flow between the placenta and fetus after misoprostol administration. The absolute risk of these malformations appears to be low (less than 10 per 1,000 births exposed to misoprostol *in utero*).[69,70]

These findings highlight the importance of informing clinicians and women of the potential risks of misoprostol use and the need—where possible—to provide surgical abortions when misoprostol is used to induce abortion but is not effective. Additional data about the teratogenicity of misoprostol are needed to provide more accurate information.[69]

Implications for research and practice

While the body of literature on misoprostol use in obstetrics and gynecology has grown substantially over the past two decades, several research topics—and their implications for global health practices—still must be addressed.

More research is needed on the use of misoprostol for preventing and treating postpartum hemorrhage. Given the high mortality rates associated with postpartum hemorrhage, misoprostol may be an important option where other uterotonic drugs are not available, cannot be stored properly, or are contraindicated.

Additional research is needed on the use of misoprostol for post-abortion care. Use of misoprostol after incomplete abortion (induced or spontaneous) appears to minimize the risks associated with more invasive techniques.

Health care providers—including pharmacists—need accurate information about potential misoprostol indications, regimens, side effects, and risks. Clinicians at primary- and secondary-level facilities must be trained and equipped to treat incomplete abortion and other complications. Where the drug is registered, providers should understand potential obstetric and gynecologic applications. Pharmacists, who are a primary source of misoprostol, also must have accurate information about the drug and knowledge about how to make appropriate referrals to clinicians who can provide care.

Women need accurate information about misoprostol. If informal channels are their only information source, women may receive inaccurate information about misoprostol administration and dosages. Women who self-administer misoprostol may be unable to determine if their bleeding is normal or if a complete abortion has occurred.[57] To the full extent allowed by law, programs should provide women with information they need to avoid unnecessary risks or seek necessary medical treatment. Research is needed to evaluate the most effective way of counseling women and providing them with this information.

Obtaining regulatory approval for obstetric and gynecologic indications in more countries would help standardize clinician knowledge and product access. Misoprostol registration for one or more obstetric or gynecologic indications would help ensure that clinicians are knowledgeable about the drug and recommended regimens. Inclusion on WHO's Model List of Essential Medicines and on the US Pharmacopeia, for example, would help facilitate procurement processes. National policies on misoprostol use would help standardize service delivery.

Researchers should address the research gap for the use of misoprostol to induce abortion between 10 and 12 weeks. Most studies of misoprostol-only regimens for early abortion focus on gestations through 9 weeks. Additional studies are needed to determine misoprostol's safety and effectiveness during the final weeks of the first trimester.

Conclusion

Research results indicate that misoprostol can be an effective intervention for spontaneous and induced abortion, cervical ripening, and induction of labor. Additional research is needed on its effectiveness for other obstetric and gynecologic indications.

The benefits of misoprostol use could be particularly relevant for low-resource settings, where women face significant morbidity and mortality from unsafe abortion and a lack of adequate obstetric care. If misoprostol is to be safely used in these settings, women and health care providers need clear and uniform guidelines. With evidence-based information on misoprostol administration, health care providers could save the lives of thousands of women who would otherwise undergo unsafe interventions or no interventions at all.

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