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INTRODUCTION

Misoprostol in obstetrics and gynecology

Although misoprostol is generally not registered for reproductive health use, it is widely used by gynecologists and obstetricians. In a survey on the use of misoprostol conducted in three contrasting countries (Brazil, Jamaica and the USA), 61% of obstetricians and gynecologists stated that they used it to evacuate the uterus after intrauterine fetal death, 57% used it for missed abortions, and 46% to induce labor [1]. Its popularity may be accounted for by the fact that it is as effective as the best available prostaglandin at softening the cervix and producing contractions of the uterus, while at the same time being low-cost and heat-stable.

The absence of registration for its obstetrical and gynecological applications is an important problem. The pharmaceutical industry is normally responsible for informing physicians about drugs' indications, effectiveness, correct dosages, route of administration, dosage interval, contraindications, precautions, side-effects and management of complications. However, as misoprostol is generally not registered for reproductive health indications, the industry has neither provided this information for physicians nor packaged the drug in appropriate dosages. The result is that this drug is used in many different ways according to informal local protocols. While this may not be a serious problem in early pregnancy, the use of too high a dose in late pregnancy can have serious consequences. In induction of labor, for example, too high a dose of misoprostol may cause uterine hyperstimulation and rupture of the uterus, thus jeopardizing the life of the mother and of the fetus [2–4].

Misoprostol is an analogue of prostaglandin E1 (PG E1) which was registered in many countries during the second half of the 1980s under the proprietary name Cytotec (Pharmacia), for the treatment of peptic ulcers, particularly those caused by non-steroidal anti-inflammatory drugs [5–7]. Its use for this purpose is contraindicated for pregnant women as it may cause uterine contractions and miscarriage.

In Brazil, as in many other countries where abortion is illegal, employees of retail pharmacies are accustomed to selling a wide range of drugs to "bring on periods". In the 1980s they realized that the uterine "side-effect" of Cytotec made it a highly effective drug for "bringing on periods" in cases of delayed menses. The knowledge that misoprostol was very effective at causing abortions spread rapidly and, by the end of the 1980s, a high proportion of clandestine abortions in Brazil were induced by misoprostol [8,9]. Similar experiences have been described in other Latin American countries [10].

Misoprostol's undisputed ability to bring on uterine contractions led to it being evaluated as a means of inducing abortion or labor with a dead [11,12] or live [13–18] fetus, or to interrupt pregnancy [19–22]. Its potential was especially promising in the developing world where maternal mortality is high and where an effective, low-cost and stable prostaglandin is urgently needed. The benefits of misoprostol in settings with few resources have since been widely demonstrated. It has been possible to reduce failed inductions and the proportion of cesarean sections [3,23–28], and it has facilitated the difficult challenge of evacuating a dead fetus during the second trimester of pregnancy, substituting methods that carry a high risk of morbidity and mortality [29,30]. It has also proved its capacity to prevent postpartum hemorrhage in situations where oxytocin is not available or may lose effectiveness due to high ambient temperatures [31,32], and there is also now evidence to correlate the increase in its use with the reduction of morbidity and mortality associated with abortion in countries with restrictive laws [10,33–35].

In spite of all these advantages, misoprostol has not been approved for use in gynecology or obstetrics in most countries. However, there are signs that health regulators are embracing the use of misoprostol. In 2003, the use of misoprostol in combination with mifepristone was approved by the United States Food and Drug Administration for the induction of abortion [36], and misoprostol has been added to the World Health Organization (WHO) Model List of Essential Drugs for the induction of labor and abortion [37]. In 2006, the government of Nigeria registered misoprostol for the prevention and treatment of postpartum hemorrhage, and a national distribution program is underway in Ethiopia (see www.venturestrategies.org). Furthermore, Pharmacia's exclusive rights to misoprostol ran out in 2005, and a number of generic alternatives to Cytotec are now being produced. Misoprostol 200 μg tablets are now produced in France, China, Brazil and Taiwan, and 25 μg vaginal pessaries are available in Brazil and Egypt (see www.misoprostol.org for links).

The absence of clear guidance relating to use of misoprostol in gynecology and obstetrics has meant that physicians and their patients run the risk of inappropriate

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use, with potentially severe consequences for both woman and fetus. It also places the attending physicians at risk of litigation as, in the absence of a license for use in pregnancy, legal liability rests with the prescriber.

1. Use of drugs other than for approved indications

Use of drugs for indications other than those approved ('off-label' use) is common practice in obstetrics [38]. In a recent study of 17,000 consecutive antenatal prescriptions in a large UK government hospital, only 1% of drugs were unlicensed [39]. However, 75% of all prescriptions were 'off-label', most of which would be considered safe for use in pregnancy. They included betamethasone (for the prevention of respiratory distress syndrome in premature neonates), erythromycin (for the prevention of chorioamnionitis after ruptured membranes) and magnesium sulfate (for eclampsia). Only 10% of the drugs prescribed were considered high risk. 'Off-label' therapy is also accepted, for example, by the United States Food and Drug Administration, which stated, "*Good medical practice and the best interests of the patient require that physicians use legally available drugs … 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*" [40].

Our objective in publishing the essential points of our existing knowledge about the use of misoprostol in gynecology and obstetrics in this supplement is to enable practitioners to use the drug safely outside the approved indications, while being *well informed about the product, to base its use on firm scientific rationale and on sound medical evidence*. Guidelines for misoprostol use in reproductive health are available in South America [41] and on the internet (www.misoprostol.org) but it is hoped that this supplement will make knowledge about optimal misoprostol dosages more widely available.

2. Contents of the supplement

This supplement is designed to provide guidance to help our fellow gynecologists and obstetricians to take decisions on treatment for a number of specific conditions. This requires an evaluation of the evidence and a weighing up of the potential risks and benefits of the drug's use in each specific situation.

Misoprostol has a large number of potential uses. In this supplement, a team of experts has assessed the existing evidence and has suggested an optimal dose and route. In clinical practice, however, it is for each physician to decide how best to apply it in his or her own practice, depending on the circumstances of each individual case [42].

In an effort to include the different uses of misoprostol in gynecology and obstetrics, this supplement includes the following articles: "pharmacokinetics and basic science"; "cervical priming"; "induced abortion in 1st trimester"; "induced abortion in 2nd trimester"; "incomplete abortion"; "missed abortion"; "early embryonic loss"; "intrauterine fetal death"; "induction of labor with a live fetus", and

Table 1 Misoprostol dosages for reproductive health

Indication	Dosage	Notes
Induced abortion (0–12 weeks)	800 μg vaginally 12-hrly	Ideally used 48 h after mifepristone 200 mg
Missed abortion (0–12 weeks)	Vaginal misoprostol 800 μg stat or sublingual misoprostol 600 μg	Leave to work for 1–2 weeks (unless heavy bleeding or infection)
Incomplete abortion (0–12 weeks)	600 μg orally stat	Leave to work for 2 weeks (unless heavy bleeding or infection)
Induced abortion (13–24 weeks)	400 μg vaginally 3-hrly	Use 200 μg only in women with cesarean scar. Ideally used 48 h after mifepristone 200 mg
Intrauterine fetal death (>24 weeks)	13–17 weeks: 200 μg 6-hrly 18–26 weeks: 100 μg 6-hrly 27–43 wks: 25–50 μg 4-hrly	Reduce doses in women with previous cesarean section
Induction of labour (live fetus >24 weeks)	25 μg vaginally 4-hrly OR 50 μg orally 4-hrly	Do not use if previous cesarean section
PPH prophylaxis	600 μg orally stat	Not as effective as oxytocin or ergometrine. Exclude second twin before administration. Do not repeat within 2 h
PPH treatment	600 μg orally stat	Limited evidence for benefit — use conventional oxytocics first
Cervical ripening prior to instrumentation	400 μg vaginally 3 h before procedure	Use for insertion of intrauterine device, surgical termination of pregnancy, dilatation and curettage, hysteroscopy

Wallchart with summary of misoprostol dosages for reproductive health indications (stat = single dose taken immediately, PPH = postpartum hemorrhage) International Journal of Gynecology and Obstetrics 2007

"prevention and treatment of postpartum hemorrhage". A summary table of the recommended dosages in each chapter is given in Table 1.

Some concepts are repeated in all articles, such as contraindications for the use of misoprostol. This is done so that each article can be consulted independently from the others. The exception is drug pharmacology, which called for a whole separate chapter. For the sake of brevity, we give no specific guidance on counseling before the drug's use. However, it should be taken as read that all patients will benefit from receiving information about the likely course of the treatment and possible side-effects.

No attempt has been made to classify the strength of the evidence available for each indication. However, all statements about the use of misoprostol in this supplement have been agreed by the authors and submitted to the scrutiny of other external experts. The papers on each indication were written by misoprostol experts brought together by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) for a meeting in Bellagio, Italy in February 2007. Funding for the meeting was provided from various sources including HRP, the Rockefeller Foundation, Gynuity Health Projects and Ipas.

We are aware that some of the recommended doses, routes of administrations and intervals between doses may change in the future, when further evidence becomes available. This is just part of medical history. The combined contraceptive pills used today are considerably better than the original pills of the 1950s, but millions of women benefited from those early "imperfect" pills.

The intention of this publication is to make accessible to our colleagues throughout the world a synthesis of the current knowledge on the use of this drug. It is hoped that this will avoid dangerous misuse and improve practice with a view to reducing maternal morbidity and mortality.

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A. Weeks
Guest Editor
University of Liverpool, Liverpool, UK

A. Faúndes
State University of Campinas (UNICAMP), Campinas, SP, Brazil
E-mail address: afaundes@unicamp.br.