The benefit and risk of misoprostol use: in obstetrics and gynecology

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ABSTRACT

Misoprostol is licensed to treat gastric ulcers but now it is widely used for a variety of indications in obstetrics and gynecology. This is called ‘off-label’ use. Misoprostol is cheap, stable at room temperature and easily to access it. Available in tablet form, it can be administred vaginally, rectally, sublingually and buccally. This review explains benefit and risk of misoprostol in obstetric and gynecology field.

INTRODUCTION

Misoprostol is a synthetic prostaglandin E1 analogue which has a capability to produce a dose-related inhibition of gastric acid and pepsin secretion, and to enhance mucosal resistance to injury so that this drug has been approved by Food and Drug Administration in the United States (US) for the prevention and treatment gastric ulcers resulting from chronic administration of non-steroidal anti-inflammatory drugs. However, In the practice of obstetrics and gynecology, misoprostol has been used off-label for several indication, including abortion, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage. Due to misoprostol has so many benefit in the practice of obstetrics and gynecology, it is recommended by World Health Organization (WHO) as one of method for medical abortion. In 2002, Food and Drug Federation (FDA) was removed pregnancy from the label as an absolute contraindication to misoprostol use.

CHEMICAL STRUCTURE AND PHARMACOKINETIC OF MISOPROSTOL

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analogue of the naturally occurring prostaglandin E1. Misoprostol con-
tains approximately equal amounts of the two diastereomers (Figure 1). Misoprostol has 382.53412 g/mol molecular weight (MW). Misoprostol is a water-soluble, viscous liquid. Misoprostol is available in either 100 mcg or 200 mcg tablet dosage forms. There is no doses and dosing interval data of misoprostol used for any obstetrics gynecology indication that we can find in the FDA label of misoprostol because misoprostol is licensed only for treating gastric ulcer. The doses and dosing intervals were usually derived empirically from clinical trials. Misoprostol is only available in tablet form and even though misoprostol is formulated for oral use, this drug can be absorbed vaginally, sublingually, buccally and rectally. One of pharmacokinetic study reported oral misoprostol tablet can be absorbed by both rectal and vaginal routes in early pregnancy. Rectal route absorption curve is similar with vaginal route but rectal route bioavailability is lower than vaginal route. Misoprostol is absorbed best when administered vaginally.

**BENEFIT OF MISOPROSTOL IN OBSTETRY AND GYNECOLOGY PRACTICES**

Misoprostol has been extensively studied in reproductive health. Several studies showed misoprostol is very effective for some indications such as medical abortion, induction of labor, postpartum hemorrhage.

**Termination of first and second-trimester pregnancy**

World Health Organization (WHO) estimates that 210 million women worldwide become pregnant/year and about two-thirds of them deliver live infants. The remaining one-third of pregnancies end in miscarriage, stillbirth, or induced abortion. A medical abortion is a way to end a pregnancy using medications. There are several medicine which is usually used for medical abortion including mifepristone, methotrexate, misoprostol and the combination of miferistone and misoprostol. Many studies has investigated effectiveness of misoprostol in medicine abortus, especially in a way of route administration of misoprostol interest, in which the route of administration misoprostol becomes important to affect the effectiveness of misoprostol. Vaginal administration is the most effective followed by sublingual with oral being the least effective. Sublingual misoprostol must be administered more frequent (every 3 hours) to achieve a similar effectiveness to the vaginal route, but sublingual misoprostol appears to be more acceptable for women requiring treatment for medical abortion. Faundes et al reported that the 800 mcg of vaginal misoprostol administered every 12 hours for a maximum of three doses is recommended for termination of pregnancy up to 12 weeks. The recommended regimen for termination of second trimester pregnancy has been found in a retrospective study in which the regimen of 200 mg oral misoprostol at 6-hour intervals following a 200 mg or 400 mg priming vaginal dose is feasible and efficacious for second trimester pregnancy termination.

Misoprostol is not only effective when used alone, but misoprostol also effective when used with mifepristone to terminate early pregnancy. Lin et al reported that oral mifepristone 200 mg followed by sublingual administration of misoprostol 600 μg 48 hours later resulted in a complete abortion rate of 98.5% of pregnancies ≤ 49 days’ gestation, with tolerable side effects and a high satisfaction rate of 89.9%.

One of a prospective observational study has concluded that there are several predictors for successful misoprostol therapy for early pregnancy failure, such as (1) active vaginal bleeding and/or localized abdominal cholic, (2) Nulliparity or low parity not more than one, (3) Detectable vascularity by color doppler imaging (CDI) in the presumed intervillous space of missed miscarriage or anembryonic pregnancy and avascular trophoblastic tissue of incomplete miscarriage. El khali
et al found evidence that the success rate of first-dose of vaginal misoprostol (800 µg) may reach >97% in missed miscarriage and 100% with anembryonic pregnancy in woman with early pregnancy failure presenting with a combination of active vaginal bleeding and/or abdominal colic combined with parity 0–1.\textsuperscript{13}

### Induction of labor

Induction of labour is the initiation of labour using artificial means in a pregnant women with the aim to achieve vaginal delivery within 24 to 48 hours.\textsuperscript{14,15} This is a common procedure in obstetrics. The indication for this procedure including (1) Pregnancy beyond term, (2) Prelabour premature ruptur of membrane, and (3) Fetal anomaly or fetal death.\textsuperscript{15}

There are several methods to promote labor induction, including mechanical methods (eg, membrane stripping or sweeping, Foley catheter insertion, and amniotomy) and pharmacologic agents (eg, oxytocin and prostaglandins). Prostaglandin such as misoprostol is an agent which has been shown to be effective to induction of labour.\textsuperscript{16} Each dosage form of misoprostol has different effectiveness. Oral misoprostol is more effective than placebo and as effective as vaginal misoprostol at achieving vaginal delivery.\textsuperscript{17} As well as the dose of misoprostol is still uncertain. A meta-analysis has been performed by McMaster et al\textsuperscript{18} to prove the efficacy and safety of 25 versus 50 micrograms of intravaginal misoprostol tablets for the induction of labour and cervical ripening. They found evidence that the efficacity and safety of 25 micrograms was less efficacious than 50 micrograms of vaginal misoprostol when used for labour induction and cervical ripening. But for the safety reasons, the 25-micrograms dose makes preferable.

### Postpartum Haemorrhage

A blood loss of 500 ml or more within 24 hours after birth is commonly called as postpartum haemorrhage (PPH). PPH is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one quarter of all maternal deaths globally. PPH is the most leading cause of death and the majority of these could be avoided through the use of prophylactic uterotonic agents during the third stage of labour.\textsuperscript{19}

Active management of the third stage of labour which consist prophylactic administration of a uterotonic agent, controlled traction of the umbilical cord, and uterine massage is highly effective to reduce the risk of PPH. Uterotonic agents such as oxytocin are administered shortly following delivery of the baby to stimulate uterine contractions. WHO has recommended the use of oxytocin 10 IU as uterotonic agents during the third stage of labor for the prevention of PPH for all births. Oxytocin has been used routinely during cesarean delivery to prevent uterine atony and excessive uterine bleeding. Unfortunately, oxytocin is only available in injection form which is seldom available for births outside the health system, therefore misoprostol has attracted attention to prevent or treat postpartum haemorrhage.\textsuperscript{20}

### Risk of Misoprostol in Obstetrics and Gynecology Practices

Eventhough misoprostol has so many benefit in obstetrics and gynecology field, misoprostol has many undesirable effects. Several case study of misoprostol side effect were reported by researchers worldwide. Schoen et al\textsuperscript{21} reported A 21-year-old woman received buccal misoprostol as a ripening agent for postdate labor induction and experienced anaphylaxis and tachysystole. Misoprostol can cause high fevers and there is an evidence that genetic susceptibility may play role in misoprostol-induced fever. Alvirefic et al\textsuperscript{22} reported the role of genetic in misoprostol induced-fever. They found that The ABCC4 single nucleotide polymorphism rs11568658 may contribute with misoprostol-induced fever.

Induction with misoprostol is one of risk factors for uterine rupture even in women with no prior cesarean delivery history. A case study which is reported by Mazzone and Woolever\textsuperscript{23} found that a multigravida woman had a spontaneous uterine rupture after induction with misoprostol and oxytocin eventhough she did not have an unscarred uterus. Nuthalapaty et al\textsuperscript{24} found that high dose vaginal misoprostol (an initial 600 µg dose of intravaginal misoprostol followed by an additional 400 µg of intravaginal miso-
prostol every 4 hours) can cause side effects including post partum hemorrhage (>500 cc), isolated fever, nausea and diarrhea higher than women who received concentrated oxytocin plus low-dose vaginal PGE1 (277-1667 mU/min dose of oxytocin plus vaginal misoprostol 400 μg initially, followed by 200 μg every 6 hours for 2 doses, then 100 μg for one dose (total 900 μg)). Another study reported incidence of side effects following misoprostol treatment according to gestational age at abortion. That study found that there are differences proportion of side effects between ≤12 weeks of pregnancy with up to 12 weeks of pregnancy. Less than 10% of the women with ≤12 weeks reported side effects, which consisted of severe pain, chills, fever and diarrhea. In contrast with women with ≥12 weeks who have high side effect proportion.25

In cases of retained placenta, high dose misoprostol administered rectally does not give a promising result to expulsion of placenta within 30 minutes after rectal misoprostol administration and does not seem to decrease the rate of manual removal of placenta (MROP) under general anesthesia.26

A case of severe hypersensitivity reaction after treatment with intravaginal administration of misoprostol has been reported. Madaan et al27 reported a 32 year primigravida presented at 12 weeks of gestation with missed abortion who received intravaginal misoprostol 800μg experiences severe hypersensitivity reaction which begins with symptoms such as shivering, intense burning sensation and feeling of warmth over face, hands and feet after 20 minutes of intravaginal placement of misoprostol. This case must be kept in mind that the use of misoprostol does not rule out the possibility of the emergence of side effects.

CONCLUSIONS

Although misoprostol is not licensed for reproductive health use, it is widely used by gynecologists and obstetricians. Misoprostol has been proven to have numerous beneficial effects, including the ability to prevent and treat postpartum hemorrhage and to induce labor. However, every drug has side effects so that needs to be used with care and based on evidence based medicine.

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