



Fact sheets: Uterotonic drugs for the prevention and treatment of postpartum hemorrhage



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Prevention of Postpartum Hemorrhage Initiative (POPPHI)

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About POPPHI

The Prevention of Postpartum Hemorrhage Initiative (POPPHI) is a USAID-funded, five-year project focusing on the reduction of postpartum hemorrhage, the single most important cause of maternal deaths worldwide. The POPPHI project is led by PATH and includes four partners: RTI International, EngenderHealth, the International Federation of Gynaecology and Obstetrics (FIGO), and the International Confederation of Midwives (ICM).

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Acronyms

AMTSL	active management of the third stage of labor
CCT	controlled cord traction
EOC	essential obstetric care
HLD	high-level disinfection
IM	intra-muscular
IU	international units
IV	Intra-venous
MNH	maternal and newborn health
MPS	Making Pregnancy Safer
NGO	non-governmental organization
POPPHI	Prevention of Postpartum Hemorrhage Initiative
RCT	Randomized controlled trial
SBA	skilled birth attendant
USAID	United States Agency for International Development
WHO	World Health Organization

Uterotonic drugs

Introduction

Uterine stimulants (uterotonics or oxytocics) are medications given to cause a woman's uterus to contract, or to increase the frequency and intensity of the contractions. The three uterotonic drugs used most frequently are the oxytocins, prostaglandins, and ergot alkaloids. Uterotonic drugs may be given intramuscularly (IM), intravenously (IV), and as a tablet, gel, or suppository.

The following table outlines the uterotonic drugs included on the WHO list of essential medications.

Table 1. Uterotonic drugs

Name of Drug/ Preparation	Drug Action & Effectiveness	Side Effects & Cautions*
Oxytocin Posterior pituitary extract	- Acts within 2-3 minutes - Effect lasts about 15 - 30 minutes	- No known contraindications for postpartum use - No or minimal side effects - If used for labour induction or augmentation: do not give oxytocin until at least 6 hours after last Misoprostol dose
Misoprostol E1 analog prostaglandin	Orally: - Acts within 3-5 minutes - Peak serum concentration between 18 – 34 minutes - Effect lasts 75 minutes	- No known contraindications for postpartum use - Shivering and transient elevated temperature is common
Syntometrine Combination of 5 IU oxytocin plus 0.5 mg ergometrine	Combined rapid action of oxytocin and sustained action of ergometrine	- Same cautions and contraindications as ergometrine - Only for use in the postpartum - Side effects: nausea, vomiting, headaches and hypertension
Ergometrine Preparation of ergot	- Acts within 6-7 minutes IM - Effect lasts 2-4 hours	- Contraindicated in women with or having history of hypertension, heart disease, retained placenta, pre-eclampsia, eclampsia - Only for use in the postpartum - Causes tonic contractions - may increase risk of retained placenta - Side effects: nausea, vomiting, headaches and hypertension - Do not use if drug is cloudy or has changed color.

* Lists of side effects, cautions, and contraindications are not meant to be complete; evaluate each client for sensitivities/appropriateness before use of any drug.

Uterotonic drugs are used to induce (start) or augment (speed) labour; facilitate uterine contractions following a spontaneous abortion; prevent postpartum haemorrhage during active management of the third stage of labour; treat haemorrhage following childbirth or abortion; and for other gynaecological reasons.

Labor induction and augmentation

Medical and obstetrical indications for and risks of labor induction and augmentation

Uterine stimulants are used to induce, or begin, labour in certain circumstances when the woman's labour has not started naturally. Labor may be induced for either maternal or fetal indications. Induction of labor is undertaken when both of the following criteria are met:

- Continuing the pregnancy is believed to be associated with greater maternal or fetal risk than intervention to deliver the pregnancy, and
- There is no contraindication to vaginal birth.

The magnitude of risk is influenced by factors such as gestational age, presence/absence of fetal lung maturity, severity of the clinical condition, and cervical status. Some examples of common medical and obstetrical conditions for which induction may be indicated include chorioamnionitis, foetal demise, pregnancy-induced hypertension, premature rupture of membranes, postterm pregnancy, maternal indications (e.g., diabetes mellitus, renal disease, chronic pulmonary disease, chronic hypertension), foetal compromise (e.g., severe foetal growth restriction, isoimmunisation), preeclampsia, and eclampsia.¹

Augmentation refers to stimulation of uterine contractions when spontaneous contractions have failed to result in progressive cervical dilatation or descent of the foetus. Uterine stimulants can be used to augment existing uterine contractions, to increase their frequency, duration and strength, when labour is not progressing well. If **contractions are inefficient** and **cephalopelvic disproportion and obstruction have been excluded**, the most probable cause of prolonged labor is inadequate uterine activity. Augmentation should be considered if the frequency of contractions is less than 3 contractions per 10 minutes,² each lasting less than 40 seconds,³ accompanied by failure of labour to progress.

Risks of induction and augmentation include: failure of induction and uterine hyperstimulation. Uterine hyperstimulation may result in compromised utero-placental perfusion, abruptio placentae, foetal hypoxia or asphyxia, and uterine rupture. All of these may necessitate a need for emergent caesarean operation. Water intoxication can occur with high concentrations of oxytocin infused with large quantities of hypotonic solutions. The antidiuretic effect usually is observed only after prolonged administration with at least 40mU of oxytocin per minute. **Induction and augmentation of labour have been shown to be contributing factors to uterine atony after birth of the baby.**^{4,5}

Conditions for use of uterotonic drugs for induction and augmentation

Any health worker administering or dispensing a uterotonic drug should be authorized to do so and be trained in the proper use of the drug and management of side and adverse effects.

Labour induction and augmentation should only be attempted after:

- weighing risks and benefits of induction or augmentation.
- performing a careful assessment of the woman and foetus.

- carefully counselling the woman regarding the indications for induction or augmentation, the agents and methods of labour stimulation, and the possible need for repeat induction or caesarean delivery.

Labour induction and augmentation should only be attempted in facilities where:

- a caesarean operation can be performed in case of maternal or foetal distress.
- personnel are available and skilled to consistently re-evaluate and document the woman's and foetus' condition.
- personnel are available and skilled to promptly recognize and manage an abnormal change in either the woman's or foetus' condition.

The pregnant woman should be monitored closely during induction or augmentation of labour or cervical ripening and the woman should never be left alone.

Clear documentation of administration of any uterotonic drugs should be part of the woman's medical record. Documentation includes the time, route, and dosage of any medications given, as well as a record of any side effects.

Uterotonic drugs used for induction and augmentation of labor

Oxytocin and misoprostol are the uterotonic drugs most commonly used for induction and augmentation of labor. Refer to national or facility-based protocols for dosages and regimen.

Safety concerns when using uterotonic drugs to induce or augment labor

When using oxytocin for induction or augmentation of labour:

- Never administer oxytocin intramuscularly (IM) during labor.
- Do not give oxytocin for further induction or augmentation until at least 6 hours after last misoprostol dose.

When using misoprostol for induction or augmentation of labour:

- Use 25 mcg tablets. When 25 mcg tablets of misoprostol are not available, do not break higher dose tablets (usually 200 mcg) and administer for induction. When 200 mcg tablets are broken, the exact dose of misoprostol being give to the woman is not reliable and could be dangerous. If more than 25 mcg of misoprostol is administered during labor, this could cause a uterine rupture and / or the death of the baby.

Prevention of postpartum hemorrhage (PPH)

Medical and obstetrical indications for administering uterotonic drugs for active management of the third stage of labor (AMTSL)

AMTSL should be offered routinely to all women by all skilled birth attendants. Active management involves a group of interventions that include administration of a prophylactic uterotonic after delivery of the baby, controlled cord traction to deliver the placenta, and uterine massage after delivery of the placenta to decrease the incidence and severity of postpartum haemorrhage.

- **Administration of a uterotonic drug** stimulates uterine contractions that facilitate separation of the placenta from the uterine wall resulting in rapid delivery of the placenta and stimulates uterine contractions that compress maternal blood vessels at the placental site after delivery of the placenta

- **Controlled cord traction** (CCT) facilitates rapid delivery of the placenta and emptying of the uterus
- **Uterine massage** after delivery of the placenta stimulates uterine contractions and removes clots that may inhibit uterine contraction.

Active management is associated with a lower incidence of blood loss, postpartum haemorrhage (PPH), need for blood transfusion, prolonged third stage of labour, and maternal anaemia. There are no apparent adverse effects of AMTSL on the baby.

Conditions for use of uterotonic drugs for the prevention of PPH

Any health worker administering or dispensing a uterotonic drug should be authorized to do so and be trained in the proper use of the drug and management of side and adverse effects.

Clear documentation of administration of any uterotonic drugs should be part of the woman's medical record. Documentation includes the time, route, and dosage of any medications given, as well as a record of any side effects.

Uterotonic drugs used for AMTSL / prevention of PPH

The uterotonic drug of choice for AMTSL is oxytocin 10 IU IM.

In the context of AMTSL, if oxytocin is available:

- Skilled attendants should offer oxytocin to all women for prevention of PPH in preference to ergometrine/methylergometrine.

This recommendation places a high value on avoiding adverse effects of ergometrine and assumes similar benefit for oxytocin and ergometrine for preventing PPH⁶.

- Skilled attendants should offer oxytocin for prevention of PPH in preference to oral misoprostol (600 mcg).

This recommendation places a high value on the relative benefits of oxytocin in preventing blood loss compared to misoprostol, as well as the increased adverse effects of misoprostol compared to oxytocin⁶.

In the context of AMTSL, if oxytocin is not available but other injectable uterotonics are available:

- Skilled attendants should offer ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine to women without hypertension or heart disease for prevention of PPH⁶.
- Skilled attendants should offer 600 micrograms (mcg) misoprostol orally for prevention of PPH to women with hypertension or heart disease for prevention of PPH⁷.

In the context of AMTSL, if injectable uterotonic drugs are not available, skilled attendants should offer 600 micrograms (mcg) misoprostol orally for prevention of PPH.^{6,7}

When controlled cord traction cannot be performed, administration of oxytocin or misoprostol within one minute of the baby's birth will still stimulate uterine contractions that will facilitate separation of the placenta from the uterine wall. Uterine massage may be performed after delivery of the placenta.^{6,7}

Safety concerns when using uterotonic drugs for prevention of PPH

Ergometrine is contraindicated in women with a history of hypertension, heart disease, pre-eclampsia, or eclampsia.

Treatment of PPH

Medical and obstetrical indications for administering uterotonic drugs for treatment of PPH

After the baby is born, uterine muscles contract, clamping down on the uterine blood vessels to help limit bleeding after the placenta has detached. If the muscles do not contract strongly enough, PPH can occur, which can be life-threatening. PPH from uterine atony is a serious problem that requires efficient and effective treatments to avert maternal morbidity (severe anaemia, shock, and need for emergency laparotomy for uterine artery ligation or hysterectomy) or mortality.

The earliest treatment options for primary PPH due to uterine atony include use of uterotonic drugs to increase uterine muscle contractions that compress maternal blood vessels at the site of placental separation.

Conditions for use of uterotonic drugs for treatment of PPH

Any health worker administering or dispensing a uterotonic drug should be authorized to do so and be trained in the proper use of the drug and management of side and adverse effects.

Clear documentation of administration of any uterotonic drugs should be part of the woman's medical record. Documentation includes the time, route, and dosage of any medications given, as well as a record of any side effects.

Uterotonic drugs used for treatment of PPH

Any of the uterotonic drugs (ergometrine, oxytocin and prostaglandins) can be given together or sequentially for treatment of PPH.

Safety concerns when using uterotonic drugs for treatment of PPH

Ergometrine is contraindicated in women with a history of hypertension, heart disease, pre-eclampsia, or eclampsia.

Cost comparison

The acquisition costs of oxytocin and ergometrine are essentially the same,⁸ while the fixed drug combination of oxytocin and ergometrine is likely to be more expensive in most countries than oxytocin or ergometrine alone. The price of misoprostol will depend upon the manufacturer, the supply, and the demand. The reported manufacturers' average price for misoprostol in 2007 was 12.15 ¢/200 mcg tablet.

Administration costs of oxytocin, ergometrine, and the fixed drug combination of oxytocin and ergometrine are likely to be generally equivalent. Administration costs of misoprostol will be less because it does not require a syringe and needle, a skilled birth attendant trained and authorized to administer injections, or consumables and supplies to ensure safe injection and infection prevention practices.

Storage costs may be higher for ergometrine (and the fixed drug combination of oxytocin and ergometrine) because it requires temperature-controlled transport and storage and protection from light. Oxytocin is more stable and storage costs may be less than ergometrine⁹. Costs for storage of misoprostol will be minimal as it is the most stable of the three uterotonic drugs and can be stored at room temperature.

Oxytocin: Prevention and treatment of postpartum haemorrhage

Note: Information on the use of oxytocin for induction and augmentation of labor can be found in: PATH, the World Health Organization, and the United Nations Population Fund. *Essential Medicines for Reproductive Health: Guiding Principles for Their Inclusion on National Medicines Lists*. Seattle: PATH; 2006.

Background

Postpartum haemorrhage (PPH) is the single most important cause of maternal death worldwide and one of the major causes of maternal death in developed and developing countries, and increases morbidity in millions of women who give birth. Oxytocin is used to stimulate uterine contractions to prevent and treat postpartum haemorrhage. In moderate doses, oxytocin produces slow, generalized contractions with full relaxation in between; in high doses, it produces sustained tonic contractions.

Evidence review

According to several reviews of evidence for effectiveness and safety of uterotonic drugs in the prevention of postpartum haemorrhage, oxytocin used alone has shown effectiveness in reducing the incidence of postpartum haemorrhage. The combination of ergometrine with oxytocin is slightly superior for this outcome.¹⁰ However, maternal side effects are more frequent in women treated with the combination regimen than with oxytocin alone.¹⁰ Moreover, oxytocin is recommended for prevention of postpartum haemorrhage, since it is more thermostable than ergometrine.

Presentation

Oxytocin is most often available in clear glass 1ml ampoules. Each ampoule will contain either 5 IU or 10 IU.

Oxytocin 10 IU in the Uniject™ device—a prefilled, easy-to-use, non-reusable syringe—is an advance in the method of delivering oxytocin and is currently being used in pilot studies (Figure 1). This delivery method ensures the correct dose is given with little preparation and medical waste. The benefits of this device may improve the ability of midwives and other health workers to administer oxytocin within established facilities as well as outside of hospital facilities, in emergencies, or in remote locations.



Figure 1. Uniject™ device

Indications and dosage

Prevention of postpartum haemorrhage

Administering oxytocin within one minute of the baby's birth will stimulate uterine contractions that will facilitate separation of the placenta from the uterine wall and reduce postpartum haemorrhage. Oxytocin can be administered with or without controlled cord traction.

Table 2. Dose, route, and precautions for oxytocin use for AMTSL ¹¹

Dose and route	IM: 10 units If a woman has an IV when she gives birth, the provider can either give 10 IU IM or 5 IU by slow IV injection
Precautions/ Contraindications	Before giving oxytocin, rule out the presence of another baby. If oxytocin is administered when there is a second baby, there is a small risk that the second baby could be trapped in the uterus.

Treatment of postpartum haemorrhage

If the uterus fails to contract after delivery, oxytocin can be used to stimulate uterine contractions and control postpartum haemorrhage:

Table 3. Dose, route, and precautions for oxytocin use for PPH treatment¹²

Dose and route	IV: Infuse 20 units in 1 L IV fluids at 60 drops per minute IM: 10 units
Continuing dose	IV: Infuse 20 units in 1 L IV fluids at 40 drops per minute
Maximum dose	Not more than 3 L of IV fluids containing oxytocin
Precautions/ Contraindications	Do not give as an IV bolus

Oxytocin may be used for prevention or treatment of postpartum hemorrhage if misoprostol has been used for induction regardless of when the last dose of misoprostol was administered.

Storage

The stability of a drug is defined by how well it maintains active ingredient potency (and other measures such as pH) when stored over time. Pharmaceutical companies conduct stability studies to determine the appropriate shelf-life, storage conditions, and expiration dating for safe storage of the oxytocin they produce. A manufacturer will recommend storage conditions based on the conditions under which he has performed stability studies, and will set the expiry date to be consistent with this. It is therefore important to read storage recommendations made by the manufacturer.

Misoprostol: Prevention and treatment of postpartum haemorrhage (PPH)

Background

Misoprostol is a synthetic prostaglandin E₁ (PGE₁) analogue and is an alternative drug for AMTSL and directions on its use for AMTSL is included in the International Federation of Gynaecology and Obstetrics (FIGO)/International Confederation of Midwives (ICM) statement, *Prevention and Treatment of Post-partum Haemorrhage: New Advances for Low Resource Settings*. Oxytocin is the uterotonic of choice for AMTSL;⁶ however, administration of an injection requires skills and sterile equipment for safe administration. Oxytocin may be inactivated if exposed to high ambient temperatures.⁹ Misoprostol is reportedly more stable than oxytocin and has been administered by oral, sublingual and rectal routes in several studies.¹³ Oral misoprostol is being viewed as an alternative drug for AMTSL for women delivering in low-resource settings where oxytocin and a skilled birth attendant may not be available and as a PPH treatment when used in combination with other uterotonics. It has also been suggested that providers can provide misoprostol tablets where oxytocin is not available⁶ to non-skilled providers⁷ and to women themselves for the prevention of PPH.¹⁴

Evidence summary

In prevention of postpartum haemorrhage, traditional uterotonics (oxytocin or ergot derivatives) outperform prostaglandin analogues because their onset of action is faster and, in the case of oxytocin, there are fewer side effects¹⁵. However, in situations where no oxytocin is available, birth attendants' skills are limited, or there are contraindications for use of ergometrine, administering misoprostol soon after the birth of the baby reduces the occurrence of haemorrhage^{13, 14, 15}.

Misoprostol is easier to store and administer than other uterotonics, and no cold storage is needed.

Compared with other prostaglandin analogues, misoprostol is cheaper than conventional uterotonics, can be administered by multiple routes and without a syringe, and can be stored at room temperature.

Presentation

Misoprostol is most often available in tablet form. Each tablet will contain 25, 100, or 200 mcg.

Indications and dosage

Prevention of postpartum haemorrhage: Active management of the third stage of labour (AMTSL)

In situations where ***no oxytocin is available***, administering misoprostol by mouth to the mother within one minute of the baby's birth stimulates uterine contractions that will facilitate separation of the placenta from the uterine wall. Before giving misoprostol it is important to rule out the presence of another baby (undelivered twin). If misoprostol is administered when there is a second baby, there is a small risk that the second baby could be trapped in the uterus.

The steps for administering misoprostol for AMTSL include:

- (1) Before giving misoprostol, gently palpate the woman's abdomen to rule out the presence of another baby. At this point, do not massage the uterus.
- (2) If there is not another baby, begin the procedure by giving the woman misoprostol 600 mcg orally.
- (3) Perform controlled cord traction (CCT).
- (4) Perform uterine massage after the delivery of the placenta.⁷

Prevention of postpartum haemorrhage: Use of misoprostol in the absence of AMTSL

In situations where **no oxytocin is available** or **birth attendants' skills are limited**, administration of misoprostol within one minute of the baby's birth will still stimulate uterine contractions that will facilitate separation of the placenta from the uterine wall and reduce postpartum haemorrhage. When CCT is not performed, the steps to prevent PPH include:

- (1) Before administering misoprostol, gently palpate the woman's abdomen to rule out the presence of another baby. At this point, do not massage the uterus.
- (2) If there is not another baby, begin the procedure by giving the woman misoprostol 600 mcg orally within one minute of birth.
- (3) Perform uterine massage after the delivery of the placenta.⁷

Treatment of postpartum haemorrhage

If the uterus fails to contract after delivery, misoprostol can be used to stimulate uterine contractions and control postpartum haemorrhage:

Table 4. Dose, route, and precautions for misoprostol use for PPH treatment¹²

Maximum dose and route	Rectal: Single dose of 1,000 mcg. Oral: Single dose of 600 mcg Sublingual: Single dose of 800 mcg
Continuing dose	Unknown.
Precautions/ Contraindications	None

Storage

Misoprostol is relatively heat stable and may be stored at room temperature, away from excess heat and moisture.

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