Selection of uterotonic drugs in tropical climates

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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
HLD	high-level disinfection
IM	intra-muscular
IU	international units
IV	Intra-venous
MNH	maternal and newborn health
MPS	Making Pregnancy Safer
POPPHI	Prevention of Postpartum Hemorrhage Initiative
SBA	skilled birth attendant
USAID	United States Agency for International Development
WHO	World Health Organization

Definition of a uterotonic drug

Uterotonics (also known as "oxytocics") are medications given to cause a woman's uterus to contract, or to increase the frequency and intensity of the contractions. These drugs are used to induce (start) or augment (speed) labor; facilitate uterine contractions following a spontaneous abortion; prevent postpartum hemorrhage during active management of the third stage of labor; treat hemorrhage following childbirth or abortion; and for other gynecological reasons. 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 that can be given orally, vaginally, rectally, or buccally.

Selection of a uterotonic drug for use with active management of the third stage of labor (AMTSL)

AMTSL requires the administration of a uterotonic drug immediately after birth of the newborn, and before delivery of the placenta, to prevent postpartum hemorrhage (PPH). The decision on which uterotonic to use will depend on many factors, including:

- Cost
- Efficacy
- Stability
- Response time
- Adverse effects
- Contraindications
- Requirements for administering the drug

Cost

The acquisition costs of oxytocin and ergometrine are essentially the same,[1] while the fixed drug combination of oxytocin and ergometrine is likely to be more expensive in most countries than oxytocin or ergometrine alone. Misoprostol tablets are generally less expensive than either of the injectable uterotonics.

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 ergometrine.[2] 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.

Efficacy

The evidence for comparison of oxytocin and ergometrine is based on a systematic review conducted by the WHO[3] of studies that compared ergometrine (or derivatives) and oxytocin, or ergometrine alone versus the fixed dose combination of ergometrine and oxytocin. For the outcomes related to blood loss and transfusion, the results of the trials do not show a difference between lower doses of oxytocin and the recommended dose of ergometrine. The fixed drug combination of oxytocin and ergometrine was associated with less use of additional uterotonics. The available comparisons are limited, but a major difference in the benefits of oxytocin and ergometrine appears unlikely.

The evidence for comparison of oxytocin and misoprostol is based on a systematic review conducted by the WHO[4] of studies that compared use of oxytocin and misoprostol for AMTSL. Blood loss of 1000 ml or more was increased with misoprostol when compared to oxytocin 10 IU IM; there was no statistically significant difference in the use of blood transfusion with misoprostol compared with oxytocin; but there was more use of additional uterotonics with misoprostol.

Stability

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 each drug. 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.

Because reduced potency of a uterotonic drug may have serious, life-threatening consequences, it is critically important to consider both the likely storage conditions and the stability of each uterotonic drug when choosing a uterotonic. This is particularly relevant in tropical conditions and where refrigeration and protection from light are not always available or reliable.

Two factors can influence the effectiveness of injectable uterotonic drugs: temperature and light. The stability of a number of injectable uterotonic drugs was studied by the World Health Organization (WHO) as part of a research program to reduce maternal mortality.[2] Ampoules of eleven brands of injectable ergometrine, methylergometrine, and oxytocin were stored in the dark at 4 to 8°C, 21 to 25°C, 30°C, and 50°C; and in daylight at room temperature (21 to 25°C). The amount of active ingredient was measured at 0.5, 1, 2, 3, 6, and 12 months. Their findings were as follows:

- When stored at cold chain temperatures (4 to 8°C) and in the dark, all three drugs retained acceptable amounts of the active ingredient.
- When stored at higher temperatures, oxytocin was more stable than both ergometrine and methylergometrine.
- When exposed to light, even indirect light, ergometrine and methylergometrine rapidly lost potency, while oxytocin lost negligible amounts of potency.

Misoprostol does not require special transport or storage requirements, though some manufacturers will recommend protecting the product from humidity.

Response time

The following table summarizes response time and length of action for the most commonly used uterotonic drugs. Of the injectable uterotonics, oxytocin acts the most rapidly, while ergometrine has the benefit of sustained action. The fixed drug combination of oxytocin and ergometrine combines the rapid action of oxytocin with the sustained action of ergometrine.

Oral misoprostol acts moderately quickly, within 6 minutes, and has a moderately long sustained action of 75 minutes.

Name of drug/preparation	Response time and length of action
Oxytocin	Intramuscular injection: ▪ Acts within 2 to 3 minutes. ▪ Effect lasts about 15 to 30 minutes.
Misoprostol	Orally: ▪ Acts within 3-5 minutes. ▪ Peak serum concentration between 18 and 34 minutes. ▪ Effect lasts 75 minutes.
Ergometrine	Intramuscular injection: ▪ Acts within 6 to 7 minutes. ▪ Effect lasts 2 to 4 hours.
Syntometrine	Intramuscular injection: ▪ Combined rapid action of oxytocin and sustained action of ergometrine.

Adverse effects

A comparison of oxytocin versus the fixed drug combination (5 IU oxytocin + 0.5 mg ergometrine) showed a higher rate of adverse effects in women treated with the combination drug: nausea, vomiting, and high blood pressure. A lower rate of manual removal of placenta was seen in women treated with oxytocin. Overall, ergometrine alone or in combination with oxytocin is associated with more adverse effects, especially with regard to causing high blood pressure.

Misoprostol is associated with an increase in shivering, diarrhea, and temperature higher than 38°C.

Contraindications

Misoprostol and oxytocin have no known contraindications for use with AMTSL.

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

Requirements for administration of an uterotonic drug

Administering injectable uterotonics will require:

- a health worker authorized and trained to perform injections;
- a health worked trained to recognize contraindications to ergometrine;
- consumables and supplies to ensure adequate infection prevention measures;
- consumables and supplies to ensure injection safety, including disposable needles and syringes;
- cold chain for storage in the pharmacy warehouse.

Administering any uterotonic will require

- a health worker authorized and trained to provide the drug;
- a health worker who understands the timing and dose of the drug;
- a health worked trained to recognize and manage side effects of the drugs;
- application of manufacturer-specific storage recommendations.

Recommendations for selection of a uterotonic drug for prevention of PPH

In the context of active management of the third stage of labor, if all injectable uterotonic drugs are available[4, 5]:

- 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 PPH.

- 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 oxytocin.

In the context of active management of the third stage of labor, 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 PPH[4].
- Skilled attendants should offer 600 micrograms (mcg) misoprostol orally for prevention of PPH to women with hypertension or heart disease for prevention of PPH[5].

In the context of prevention of PPH, if oxytocin is not available or birth attendants' skills are limited, misoprostol should be administered soon after the birth of the baby[5]. The usual components of giving misoprostol include:

- Administration of 600 micrograms (mcg) misoprostol orally after the birth of the baby
- Controlled cord traction ONLY when a skilled attendant is present at the birth
- Uterine massage after the delivery of the placenta as appropriate.

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