

Use of uterotonic drugs for prevention and treatment of postpartum hemorrhage in tropical climates: Guidance for essential drug and safe motherhood programs

What is a uterotonic?

A uterotonic drug stimulates uterine contractions. Drugs such as oxytocin and ergometrine (also called oxytocics) have strong uterotonic properties and have long been used to prevent or treat uterine atony and reduce the amount of blood lost during and after childbirth. In obstetric practice, they have also been widely used for cervical ripening and induction of labor. The use of a uterotonic drug immediately after the delivery of the newborn (i.e., in the third stage of labor) is one of the most important interventions used to prevent postpartum hemorrhage (PPH).

How do different storage conditions affect uterotonics such as oxytocin and ergometrine?

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. Because reduced potency of uterotonic drugs 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. Storage conditions under these circumstances vary widely and vials of uterotonic drugs are often kept on open trays or kidney dishes ready for use in the labor ward.

The stability of oxytocics is mainly affected by two factors: temperature and light. The stability of a number of injectable oxytocic drugs was studied by the World Health Organization (WHO) as part of a research program to reduce maternal mortality.¹ Ampoules of 11 brands of injectable ergometrine, methylegometrine, 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.

Oxytocin is more stable than both ergometrine and methylegometrine.

When stored at cold chain temperatures (4 to 8°C) and in the dark, all three drugs retained acceptable amounts of the active ingredient. However, when stored at higher temperatures and when exposed to light, oxytocin was more stable than both ergometrine and methylegometrine.

Visual inspection of ergometrine can detect the loss of the active ingredient. Any discoloration means that the ergometrine solution has lost potency (is less than 90 percent of its stated active ingredient).

Ergometrine and methylegometrine are very sensitive to light—they must be stored in the dark or they will likely lose their potency in a short time.

The difference in stability between these drugs was particularly critical for exposure to light. The authors found that ergometrine and methylegometrine rapidly lost potency when exposed to light, even indirect light. On average, these two drugs lost 21 percent and 27 percent of their respective potency with one month of exposure to indirect light. Oxytocin did not show any loss of potency during the same test.

The authors concluded that the stability of oxytocin is better than ergometrine or methylegometrine, mainly because oxytocin lacks the adverse effects of exposure to light.

¹ Hogerzeil HV, Walker GJA, de Goeje MJ. *Stability of injectable oxytocics in tropical climates*. Geneva: World Health Organization, 1993; WHO/DPA/93.6.

Table 1: Results of simulation studies on the stability of oxytocics under tropical conditions

	Active ingredient of injectable oxytocic drugs after one year of controlled storage				
	Brands	Batches	Mean active ingredient after 12 months storage		
			Dark, 4-8 °C	Dark, 30 °C	Light, 21-25 °C
Ergometrine	4	8	5% loss	31% loss	90% loss
Methylergometrine	4	8	4% loss	18% loss	90% loss
Oxytocin	3	6	0% loss	14% loss	7% loss

Values are mean percentage of potency loss based on initial amount of active ingredient.²

Selecting a Uterotonic

What are the differences in cost?

The prices of generic ergometrine and oxytocin are similar, and both are relatively inexpensive.

Are there differences in manufacturers?

Yes. There are considerable differences between products of different manufacturers. Therefore, it is important to carefully select the supplier and conduct frequent quality control measures.

What about the cold chain during transport and storage?

The WHO study also concluded that up to two week exposure to temperatures of 40 °C or one month at 30 °C during transport would not seriously affect the potency of any of the drugs. Therefore, brief unrefrigerated transport from overseas suppliers or from a central store within country should not significantly affect the potency of injectable oxytocics. In case refrigerated storage is not available, oxytocin and ergometrine may be temporarily stored outside the refrigerator for a maximum of three months, at not more than 30 °C.

Recommendations for Selection of Injectable Uterotonic Drugs

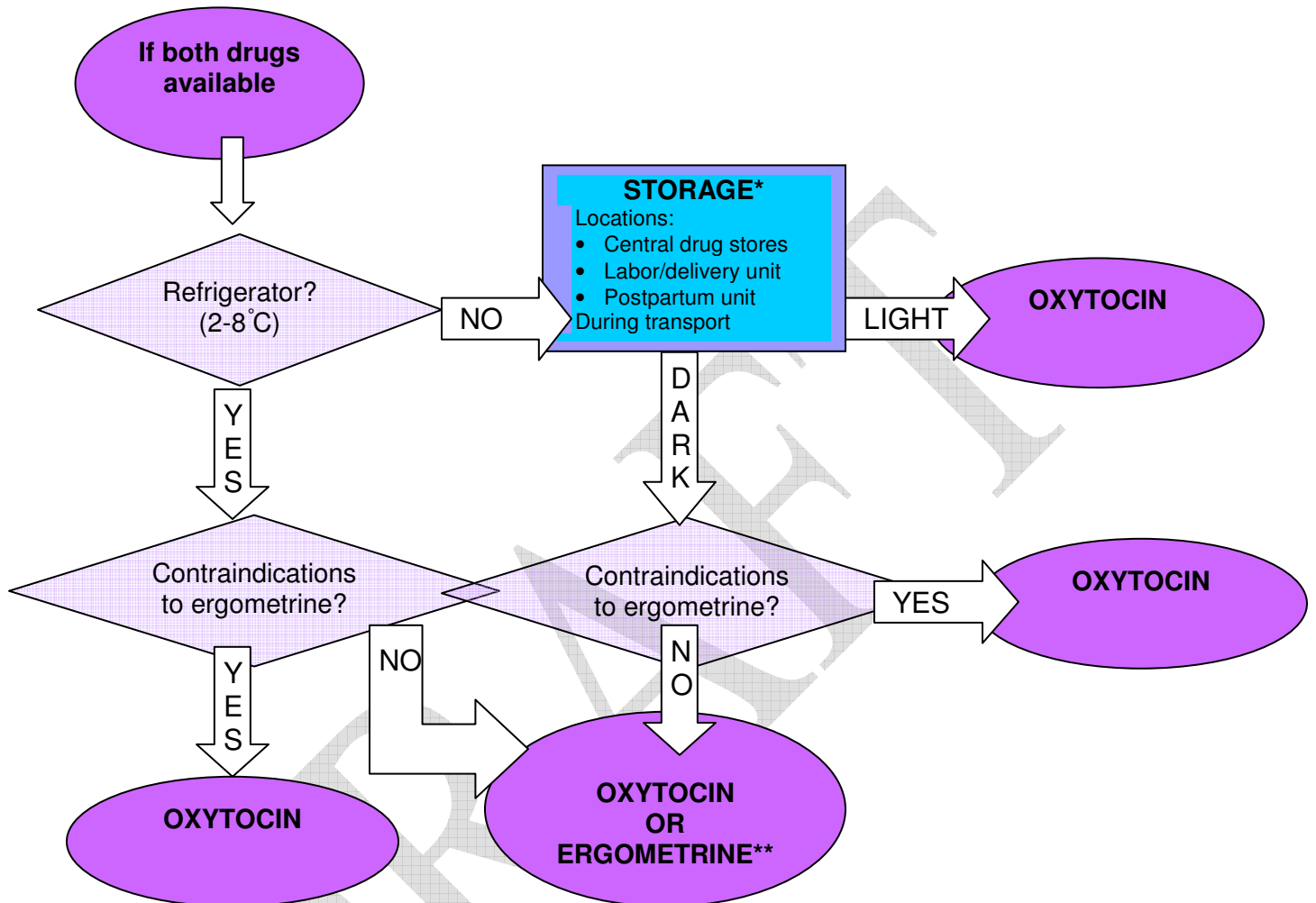
Due to its increased effectiveness, better stability, fewer contraindications and side effects, and equal cost, WHO recommends oxytocin as the drug of choice for management of the third stage of labor in developing countries. If oxytocin is not available, ergometrine may be used, as long as it is carefully stored in dark conditions.

	Oxytocin	Ergometrine
Efficacy	Very effective	Effective
Response time	Acts in 2 to 3 minutes	Acts in 6 to 7 minutes
Cost	Inexpensive	Inexpensive
Route of administration	Injection	Injection
Side effects	Minimal	Nausea and vomiting possible
Contraindications* (postpartum use)	None	Retained placenta, pre-eclampsia, eclampsia, and hypertension
Storage	Cold storage (2 to 8 °C)	Cold storage (2 to 8 °C) Protect from light
Stability	More stable than ergometrine	Very unstable in light, less thermo-stable than oxytocin

*List of contraindications is not meant to be complete; evaluate each client for drug sensitivities and appropriateness prior to the use of any drug. Only some of the major contraindications for postpartum use are listed for the above drugs.

² Hogerzeil HV, Walker G. Instability of (methyl)ergometrine in tropical climates: an overview. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 1996;69:25-29.

Flow Chart for Selecting Oxytocic Drugs



*Storage:

- Keep in closed cupboards or clean supply areas.
- Keep vials in closed box until ready for use.
- Keep out of light (including away from windows and sunlight).
- Dispense/keep adequate, accessible supply on labor/delivery and postpartum wards.
- Check ergometrine for any discoloration, since that indicates a loss of potency of drug.
- Ensure storage in a cool, dark area during transport of drugs, if possible.
- Ensure that all relevant staff are informed of guidelines on storage of uterotonics.

****WHO recommends the use of ergometrine only if oxytocin is not available.**

Guidelines for the storage of oxytocin and ergometrine

If there is:	Do the following:
<p>A cold chain</p> <ul style="list-style-type: none"> • During transit from manufacturer • During transit in-country 	<ol style="list-style-type: none"> 1. Keep oxytocics at 2 to 8°C. 2. Keep in the dark whenever possible. <p style="background-color: #e0e0e0; padding: 5px;">Oxytocin is not light sensitive, but it is still good practice to store it in the dark, if possible.</p> <p style="background-color: #e0e0e0; padding: 5px;">Ergometrine must be kept in the dark at all times; it loses potency very quickly when exposed to light.</p>
<p>No cold chain</p> <ul style="list-style-type: none"> • No reliable or consistent means of keeping drugs at required temperature during transit 	<ol style="list-style-type: none"> 1. Keep drugs in the dark, away from light during transit. <p style="background-color: #e0e0e0; padding: 5px;">If kept in the dark, drugs may be exposed for up to 2 weeks at no more than 40°C while in transit.</p>
<p>A refrigerator upon arrival at facility</p> <ul style="list-style-type: none"> • Reliable, working refrigeration <ul style="list-style-type: none"> • Able to keep a constant temperature of 2 to 8°C • Sufficient space in the refrigerator to store oxytocics 	<ol style="list-style-type: none"> 1. Store oxytocics at 2 to 8°C. 2. Keep ampoules/vials in a closed box away from light. 3. Periodically remove ample amount needed for expected client load from refrigerator. 4. Ergometrine ampoules/vials that are removed from refrigerator must be kept in the dark, out of any light. 5. Oxytocin ampoules/vials that are removed from the refrigerator can be kept in either light or dark; however, the best practice is to keep in the dark.
<p>No refrigerator upon arrival at facility</p> <ul style="list-style-type: none"> • No electricity • No reliable refrigeration • Not sufficient room in existing refrigerator to store oxytocics • No refrigeration at all 	<ol style="list-style-type: none"> 1. Keep drugs in closed boxes/cartons if possible. Remove vials/ampoules only when ready for use. 2. Keep adequate oxytocics and supplies available (needles/syringes) in labor and delivery/postpartum units at all times. 3. Store drugs in the dark, away from light. <p style="background-color: #e0e0e0; padding: 5px;">Ergometrine is very light sensitive and loses potency quickly in the light. It must be stored in dark at all times.</p> <ol style="list-style-type: none"> 4. Consider rotation of oxytocic drugs in and out of the refrigerator if space not sufficient to store entire stock. <p style="background-color: #e0e0e0; padding: 5px;">Oxytocin and ergometrine may be stored outside the refrigerator at 30°C or less for not more than 3 months.</p>
<p>Oxytocin is more stable than ergometrine, and oxytocin is not sensitive to light. WHO recommends oxytocin as the drug of choice for active management of the third stage of labor and advises that ergometrine only be used when oxytocin is not available.</p>	