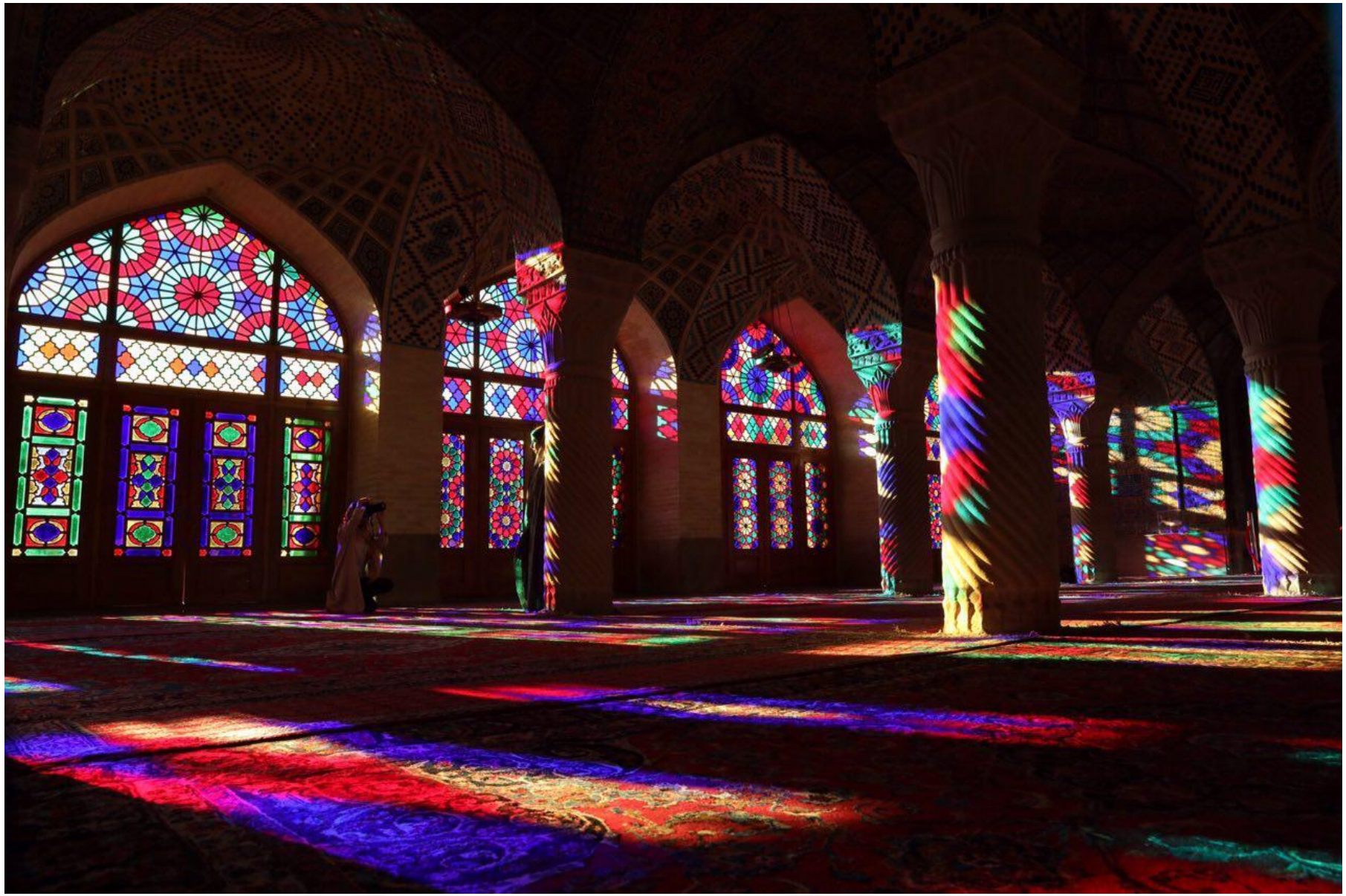

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Uterotonic Agents

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- If patient has not had an ultrasound examination, it is important to confirm the absence of an undiagnosed and undelivered twin before administering a uterotonic drug or applying controlled cord traction.

Oxytocin

- Up-to-date recommends oxytocin for active management of the third stage of labor:
- ***Timing*** : Administer oxytocin after expulsion of the infant and **before delivery of the placenta**.
- It should not be given before delivery of the anterior fetal shoulder to ensure that shoulder dystocia, if present, is not exacerbated.
- Give oxytocin before placental separation to expedite the process and continue it after placental expulsion to enhance contraction of the uterus.

- **Adverse effects are dose related :**
  - Hypotension
  - Tachycardia
  - Increased cardiac output
  - Myocardial ischemia
  - Flushing
  - Nausea, vomiting
  - Mild antidiuresis
  - Water retention and hyponatremia with large doses

- ***Route and dose*** : Intravenous infusion is preferred, but intramuscular injection is an acceptable alternative in women who do not have intravenous access.
- Avoid intravenous bolus injection because of the potential for severe hypotension.
- ***Intravenous infusion :***
  - **10 to 40 units of oxytocin per 500 mL 0.9 percent saline**
  - **Infuse 20 units of oxytocin in 500 mL 0.9 percent saline over the first hour following delivery of the placenta, subsequently infuse an additional 20 units of oxytocin in 1 L of fluid at a rate of 125 mL/hour(for 8 hours) .**
  - **Use a dose of 40 units of oxytocin in cases at high risk for hemorrhage.**

- ***Intramuscular administration :***
  - **Up to 10 units oxytocin if there is no intravenous access .**
  - Slower onset of action (3 -5 minutes versus less than 1 minute with IV)
- ***Intravenous bolus :***
  - **1 to 10 units**
  - Side effect: **significant hypotension, cardiovascular collapse and death** .
  - The minimum effective bolus dose of oxytocin appears to be **≤3 units** over 1 minute and may be as low as **0.3 units .**
  - If the initial bolus injection is not effective, **repeat once or twice** before trying a different uterotonic drug.

- **In case of uterine atony :**
  - **Oxytocin 40 units in 1 L of normal saline IV or 10 units IM (including directly into the myometrium).**
- It is not advisable to use higher doses of oxytocin (eg, up to 80 units in 500 mL over 30 minutes).
- If a high-dose oxytocin regimen is used, it is advisable to prepare smaller volumes (ie, **15 units in 250 mL**) .

- **The important point** is not the sequence of drugs, but the prompt initiation of uterotonic therapy and the prompt assessment of its effect.
- It should be possible to determine within **30 minutes.**

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Ergot Alkaloids

- ***Methylergonovine 0.2 mg intramuscularly :*** *as single agent therapy*
- ***Contraindications :***
  - Hypertension
  - History of migraine
  - Coronary or cerebral artery disease
  - Raynaud phenomenon
- ***Major disadvantages :***
  - Vomiting
  - blood pressure elevation
  - pain requiring analgesia
  - Unstable when stored unrefrigerated or exposed to light
  - **Severe HTN with concomitant use of protease inhibitors given for HIV infection**

- In a 2013 systematic review comparing prophylactic use of ergot alkaloids with oxytocin , oxytocin was superior to ergot alkaloids in preventing PPH >500 mL . Use of oxytocin was also associated with fewer side effects.
- Ergot preparations are associated with more side effects than oxytocin because they act **systemically on smooth muscle**, while oxytocin is **specific for uterine smooth muscle**.
- they are longer lasting and produce more tetanic contractions than oxytocin, thus they are particularly useful for treatment of postpartum hemorrhage.

- **In case of atony :**
  - If no hypertension or other significant arterial disease, **methylergonovine 0.2 mg** IM or directly into the myometrium (never intravenously)
  - Repeat at **two- to four-hour intervals**
- **If there has not been a good response to the first dose, quickly move on to a different uterotonic agent.**

- **Ergometrine-oxytocin (Syntometrine: 5 units oxytocin plus 0.5 mg ergometrine) :**
  - Do not have a clinically important advantage over oxytocin alone and is associated with more side effects.

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Prostaglandins

- **Route** : Oral, sublingual, rectal
- **Less effective than oxytocin or ergometrine** for active management of the third stage of labor .
- **Common side effects of misoprostol :**
  - **shivering**
  - **fever**

    Misoprostol-related fever is usually preceded by shivering, begins within 20 minutes , peaks at 1-2 hours, and declines over 3 hours . The incidence of fever varies by dose and route of administration, and is most common in high-dose sublingual misoprostol .
- Oxytocin or the combined ergometrine-oxytocin preparation is preferable to use of misoprostol .

- **Advantages**:
  - Inexpensive
  - Easy to administer
  - No refrigeration.
- **The World Health Organization (WHO) suggests using a single dose of 600 mcg orally .**
- The combined use of misoprostol and oxytocin appears to be more effective than oxytocin alone in reducing bleeding during cesarean

- **In case of atony :**
- If no asthma, **carboprost tromethamine** (15 methyl-PGF2alpha, Hemabate) **250 mcg intramuscularly every 15 to 90 minutes**, to a total cumulative dose of **2 mg (eight doses**).
- About 75% of patients respond to a single dose.
- **Move on to a different uterotonic agent if no response after one or two doses.**
- Direct injection into the myometrium either transabdominally (with or without ultrasound guidance) or vaginally **(solution of 250 mcg in 20 mL normal saline)**

- **Misoprostol (PGE1)** is most useful for reducing blood loss when injectable uterotonics are unavailable or contraindicated (eg, hypertension, asthma).
- **Sublingual :**
  - **400 mcg sublingually is preferred**
  - Rapid absorbtion
  - Peak concentration in **30 minutes** (sustained longer (**3 hours**) than with oral administration due to avoidance of first-pass hepatic metabolism)
  - **sublingual administration is probably the optimal route of administration for PPH.**
  - Other reasonable approaches : **combination of 200 mcg orally plus 400 mcg sublingually or 400, 600, or 800 mcg sublingually .**
  - **The World Health Organization suggests a single dose of 800 mcg sublingually**

- **Oral** :
  - Rapid and complete absorbtion
  - Peak concentration within **30 minutes**
  - Level is lower than with sublingual administration and declines rapidly **over 2 hours** due to hepatic metabolism.
- **Rectal :**
  - Peak concentration within **1 hour**
  - **The most commonly rectal doses are 800 and 1000 mcg**
  - Longer duration of action **(four hours)**
- **Vaginal** :
  - Not recommended
- Misoprostol can be given to women with hypertension or asthma.
- Maternal temperature should be monitored closely, and pyrexia **≥40 degrees** Celsius should be treated (eg, acetaminophen). The frequency of pyrexia increases with increasing misoprostol dose.

- **Dinoprostone (PGE2) :**
  - 20 mg vaginal or rectal is an alternative prostaglandin to misoprostol (PGE1).
  - Repeat at two-hour intervals

Oxytocin Agonists

- ***Carbetocin*** **:** A long-acting synthetic oxytocin agonist with similar pharmacologic properties to those of natural oxytocin.
- **A potential advantage:**
  - Longer duration of action
  - Similar toxicity to that of oxytocin
- **Dose: 100 mcg by a single slow intravenous injection**

•In women who underwent cesarean delivery, the use of carbetocin reduced the subsequent need for therapeutic uterotonic agents (RR 0.64, 95% CI 0.51-0.81), but not in those who underwent vaginal delivery (RR 0.93; 95% CI 0.44-1.94; one trial, 160 women).

•Carbetocin reduced the need for uterine massage postdelivery after both cesarean (RR 0.64, 95% CI 0.31-0.96) and vaginal delivery (RR 0.70, 95% CI 0.51-0.94).

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Tranexamic Acid

- An anti-fibrinolytic drug
- Useful for prevention and treatment of bleeding
- The World Maternal Antifibrinolytic Trial (WOMAN) found that tranexamic acid reduced death due to bleeding in women with postpartum hemorrhage by 20 to 30 percent, and was not associated with an increase in adverse effects.
- **Administer tranexamic acid soon after diagnosis of PPH , ideally within 3 hours of delivery, and alongside oxytocin and other uterotonics. Delay in treatment reduces the its benefit .**

- **1 gram (10 mL of a 100mg/mL solution) is infused over 10- 20 minutes, as infusion >1 mL/minute can cause hypotension. If bleeding persists after 30 minutes, a second 1 g dose may be administered. The half-life is 2 hours and the antifibrinolytic effect lasts up to 7- 8 hours in serum.**
- **Tranexamic acid should not be mixed with blood or given through a line with blood, or mixed with solutions containing penicillin.**
- **Contraindications :**
  - **Subarachnoid hemorrhage**
  - **Active intravascular clotting (DIC)**
  - **Dose reduction in patients with renal insufficiency, venous or arterial thrombosis**
- About 90% of the maternal drug is eliminated within 24 hours after IV administration. The concentration in breast milk is about 1:100 of the serum peak concentration, so it is unlikely to have antifibrinolytic effects in the infant.
- Do not administer tranexamic acid prophylactically.

Table 3. Acute Medical Management of Postpartum Hemorrhage

Drug*	Dose and Route	Frequency	Contraindications	Adverse Effects
Oxytocin	IV: 10–40 units per 500–1,000 mL as continuous infusion or IM: 10 units	Continuous	Rare, hypersensitivity to medication	Usually none. Nausea, vomiting, hyponatremia with prolonged dosing. Hypotension can result from IV push, which is not recommended.
Methylergonovine	IM: 0.2 mg	Every 2–4 h	Hypertension, preeclampsia, cardiovascular disease, hypersensitivity to drug	Nausea, vomiting, severe hypertension particularly when given IV, which is not recommended
15-methyl $PGF_{2\alpha}$	IM: 0.25 mg Intramyometrial: 0.25 mg	Every 15–90 min, eight doses maximum	Asthma. Relative contraindication for hypertension, active hepatic, pulmonary, or cardiac disease	Nausea, vomiting, diarrhea, fever (transient), headache, chills, shivering hypertension, bronchospasm
Misoprostol	600–1,000 micrograms oral, sublingual, or rectal	One time	Rare, hypersensitivity to medication or to prostaglandins	Nausea, vomiting, diarrhea shivering, fever (transient), headache

Abbreviations: IV, intravenously; IM, intramuscularly; PG, prostaglandin.

*All agents can cause nausea and vomiting.

References

- Up-to-date 2018
- ACOG bulletin 2017

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