Uterotonic medications – PPH

"It did not take her very long to die"
Ernest Hemingway. A Farewell to Arms, 1929
Uterotonic medications

✓ oxytocin  (*Syntocinon®*)
✓ carbetocin  (*T½ 6-7 times longer than with oxytocin*)
✓ methylergometrine  (*Methergin®*)
✓ prostaglandins
  ✓ misoprostol (*PGE₁ analogue*)  (*Cytotec®*)
  ✓ carboprost (*15-methyl PGF₂α*)  (*Hemabate®*)
  ✓ dinoprost (*PGE₂*)  (*Cervidil®, Minprostin®, Prostin E₂®*)
  ✓ sulprostone (*PGE₂-analogue*)  (*Nalador®*)
✓ conclusions

SOAT Tarto 7.10.2011
jouni.ahonen@fimnet.fi
Oxytocin

- the drug most commonly associated with preventable AE’s during childbirth
- the drug implicated in nearly half of all paid obstetric litigation claims
  
  *Obstet Gynecol* 2008; 112: 1279-83

- FDA black box warning “restricted to medical indications during labour”

- on the list of high-alert medications (only 12 other specific drugs)
  
Mechanism of action of oxytocin

\[ R = \text{oxytocin G-protein coupled receptor} \]
\[ G = \text{G-protein} \]
\[ \text{MLCK-P} = \text{myosin light chain kinase phosphate} \]
\[ \text{VOCC} = \text{voltage operated calcium channel} \]

Dyer et al. IJOA 2010; 19: 313-19
Mechanism of action of oxytocin

- repeated doses increasingly ineffective
- receptor desensitisation/down-regulation
- laboratory evidence of loss of oxytocin receptors during oxytocin-induced and oxytocin-augmented labour
- concentrations of oxytocin receptors and oxytocin receptor mRNA decrease
- by contrast, tonic effects of ergometrine and PGF$_{2\alpha}$ not affected by sensitisation in rat myometrium

Dyer et al. IJOA 2010; 19: 313-19
Oxytocin

✓ routine use in 3rd stage of labour reduces the incidence of PPH by 40%
  Br J Obstet Gynaecol 1997; 104: 781-6

✓ 5 IU IV or 10 IU IM (or infusion)

✓ side effects
  ✓ vasodilatation, hypotension
  ✓ myocardial ischaemia, arrhythmias
  ✓ nausea, vomiting
  ✓ headache
  ✓ flushing
  ✓ fluid retension, hyponatremia
  ✓ convulsions, coma
  Acta Anaesthesiol Scand 2009; 53: 826-7

Dyer et al. IJOA 2010; 19: 313-19
Changes in HR (A), MAP (B), and STC-VM (C) after 10 IU of oxytocin in CS and normal controls and 0.2 mg of methylergometrine in CS

ST depression
in 11/20 after 10 IU of oxytocin (CS),
in 6/20 after 0.2 mg of ergometrine (CS) and
in 5/10 after 10 IU of oxytocin (controls)
All related to oxytocin administration

Recordings of scalar ECG and VCG in one OXY-CS woman after 10 IU of oxytocin IV

ST depression at CS and the relation to oxytocin dose – A randomised controlled trial

ST depression
in 5/52 (7.7%) after 5 IU of oxytocin and
in 11/51 (21.6%) after 10 IU of oxytocin
68% related to oxytocin administration

Jonsson et al. BJOG 2010; 117: 76-83
Oxytocin in caesarean section

**Prophylaxis**
- non-labouring women $ED_{90} = 0.35$ IU
- during labour $ED_{90} = 2.99$ IU
  - “Rule of threes”
- 3 IU over $\geq 15$ sec
- repeat after 3 min if necessary
- up to 3 doses

**Treatment**
- bolus doses of $\leq 5$ IU
- RCOG 40IU/500ml 125 ml/h “rapid infusion”

Tseng and Balki *IJOA* 2010; 19: 243-45
Misoprostol (PGE$_1$)

- less effective than oxytocin for prevention of PPH
- first-line agent in settings where oxytocin not available
- thermostable, can be taken orally, fairly inexpensive
- 400-600 µg sublingually/orally
- 800-1000 µg rectally

Gülmezoglu et al. Lancet 2001; 358: 689-95
Dyer et al. IJOA 2010; 19: 313-19
Misoprostol (PGE₁)

- side effects
  - dose dependent
  - typical for prostaglandins
  - shivering
  - temperature elevation
  - nausea and/or vomiting
  - diarrhea

- no benefit in addition to injectable uterotonics for PPH in vaginal delivery

Dyer et al. IJOA 2010; 19: 313-19
Methylergometrine

- via calcium channel? $\alpha$-receptor?
- 0.2 mg IV (can be repeated ad 1 mg, WHO)
- $T_{1/2}$ 120 min
- haemodynamic responses
  - SAP increases by 11% (0.2 mg IV)
  - PAP and wedge pressure increase by 30%
  - coronary artery spasm – 8 reported AMI, most of them with inappropriate use
  - contraindicated in preeclampsia, HA, CAD
- concomitant use of CYP3A4 inhibitors!

Dyer et al. IJOA 2010; 19: 313-19
Carboprost (15-methyl PGF$_{2\alpha}$)

✓ 250 µg IM every 15 min (max 8 doses)
✓ side effects (shivering, fever, vomiting and diarrhea)
  ✓ bronchoconstriction
  ✓ ventilation-perfusion mismatch, hypoxaemia
  ✓ be aware in preeclampsia
✓ IV use contraindicated (only limited experience)
✓ not licensed for intramyometrial use

Dyer et al. IJOA 2010; 19: 313-19
Sulprostone, synthetic PGE$_2$

- Intravenous infusion of
  - 500 µg in 60 min
  - 500 µg in 3 hours
  - 500 µg in 10-12 hours
- Max 1500 µg / 24 hours
- Side effects (those already listed plus)
  - Myocardial ischaemia, cardiac arrest
  - Pulmonary oedema

Karpati et al. Anesthesiology 2004; 100: 30-6
Sulprostone, synthetic PGE$_2$

✓ contraindications
  ✓ asthma bronchiale
  ✓ cardiac diseases
  ✓ severe hypertension
  ✓ severe renal or liver insufficiency
  ✓ convulsions
  ✓ prior uterine surgery
  ✓ should not be infused into the cervix or the uterine muscle

✓ restore hypovolaemia before administering sulprostone!
1. Prophylactic administration of oxytocin

2. Early diagnosis of PPH

- Call for help: obstetric and anaesthetic joint management
- Maternal monitoring as needed:
  - Large bore venous access
  - Full blood count, coagulation screen
  - Intravenous fluids
  - Supplemental oxygen

Placenta expelled

- Examination of uterine cavity
- Manual removal of placenta

Placenta not expelled

- OXYTOCIN: 5 to 10 units, slow i.v. bolus
  - Followed by 20 units in 120 min, i.v. infusion
- 25 units slow i.v. bolus
- Empty bladder
- Uterine massage
- Examination of cervix and vagina

Persistent PPH ≥ 20 min

- SULPROSTONE: Intravenous infusion with a syringe pump within 20-30 min of onset of bleeding. 500 µg in 50 ml. Start dosage according to clinical situation and severity of PPH:
  - Initial speed: between 100 and 500 µg/h (10 to 50 ml/h)
  - Increase every 15 min by a total of 10 ml/h
  - Or initial speed: 500 µg/h (60 ml/h) and then reduce progressively by steps of 10 ml/h

But never exceed 50 ml/h and 1500 µg/24 h

- After sulprostone, continue with oxytocin i.v. infusion. 20 units in 1 h
- Examine cervix and vagina if persistent doubt

Prostaglandin not recommended

Persistent PPH

- Vaginal delivery
- Caesarean delivery

- No embolisation facility
  - Haemodynamic instability

Embolisation

Failure

- Surgery
  - Arterial ligation
  - Conservative uterine surgery
  - Hysterectomy

Dupont et al. IJOA 2009; 18: 320-27
Uterotonics – conclusions

✓ crazy doses of oxytocin must be avoided
✓ misoprostol less effective than oxytocin but a role as first-line agent exists
✓ benefit of misoprostol in addition to standard injectable uterotonics not proven but still under extensive investigation
✓ methylergometrine still a useful adjunctive agent
✓ appropriate use of sulprostone is life-saving
Thank you!