



5-7 сентября 2018 / Санкт-Петербург  
September 5-7, 2018 / St. Petersburg



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**Optimizing Cesarean Delivery Oxytocin & Uterotonic Agent Use**



# Oxytocin: Learning Objectives

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Upon Completion of this Learning Activity, Participants Should Be Able To:

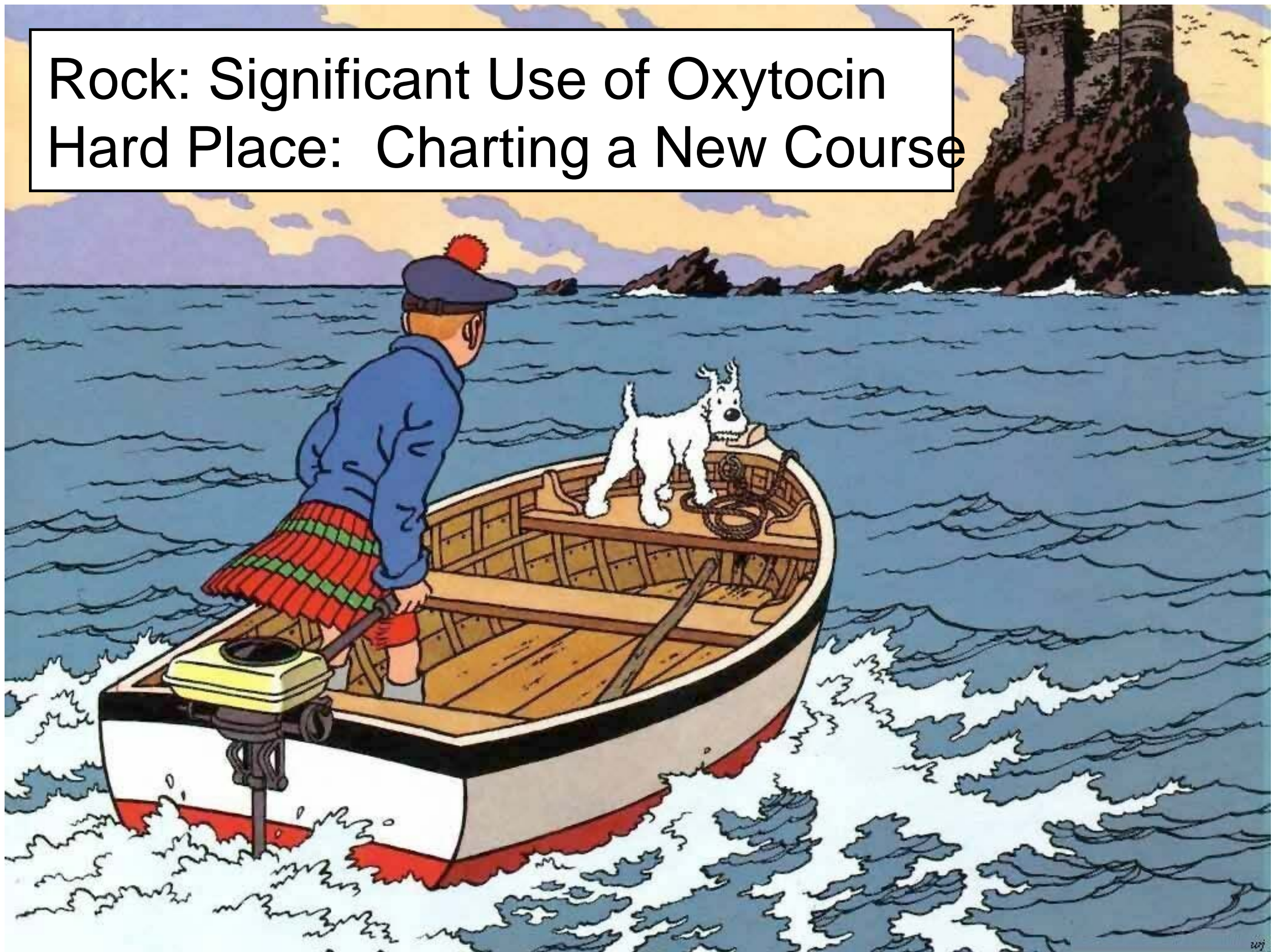
- Describe the **current state of guidance** for oxytocin use during cesarean delivery
- Review the **benefits and risks** associated with oxytocin use
- Identify an **algorithm to optimize** oxytocin and uterotonic use during cesarean delivery





# Rock: Significant Use of Oxytocin

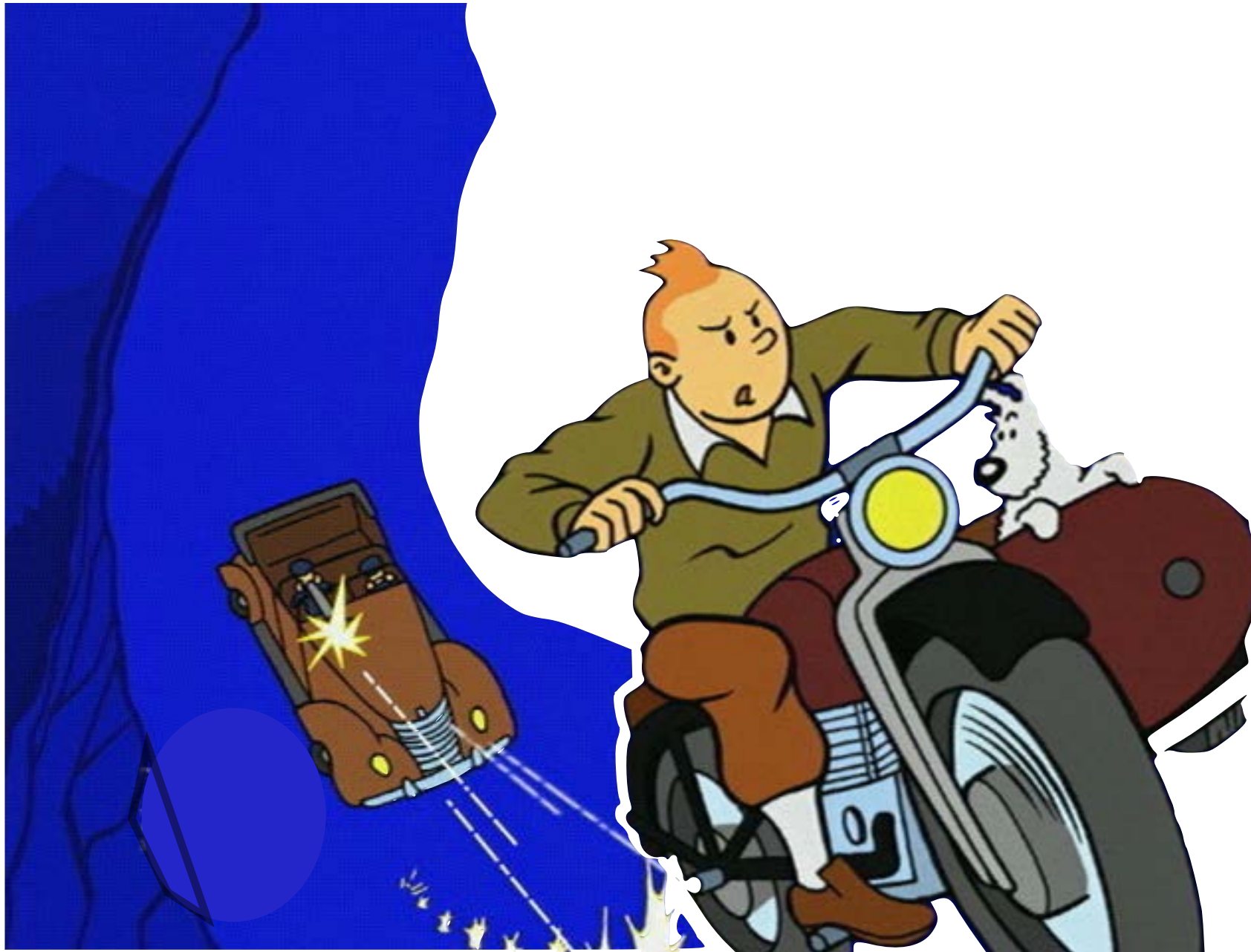
## Hard Place: Charting a New Course





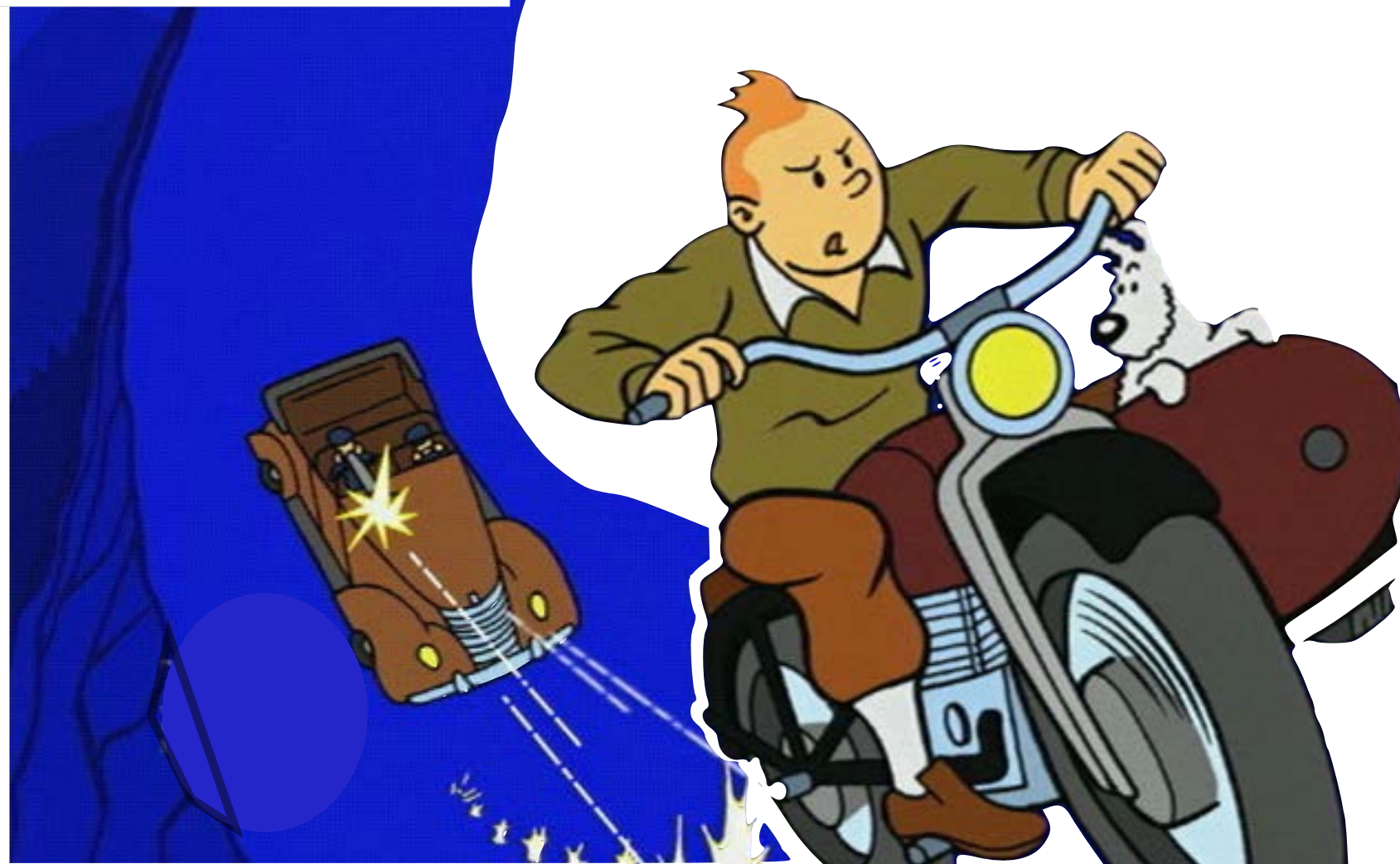
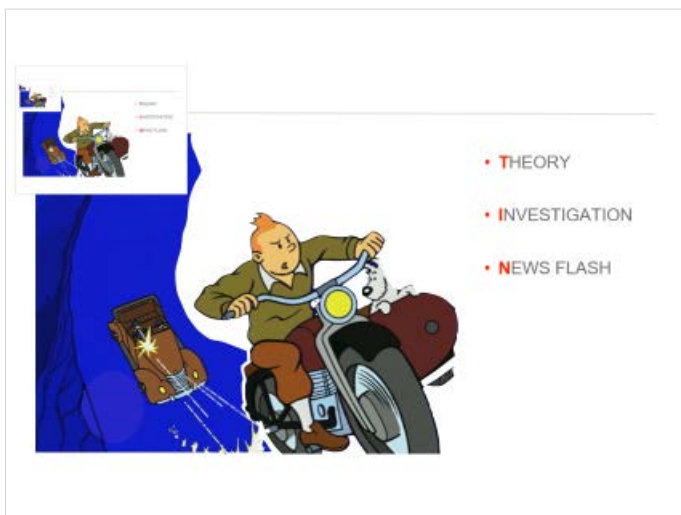
# Oxytocin

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- THEORY
- INVESTIGATION
- NEWS FLASH

No Disclosures



- THEORY
- INVESTIGATION
- NEWS FLASH

# Oxytocin

## Natural Nonapeptide

- Synthesized Hypothalamus, Secreted Posterior Pituitary
- Phospholipase C Pathway leads to  $\text{Ca}^{2+}$  influx
- Pregnant physiologic levels:  $10^{-10}$  mol/L

## Synthetic Octapeptide

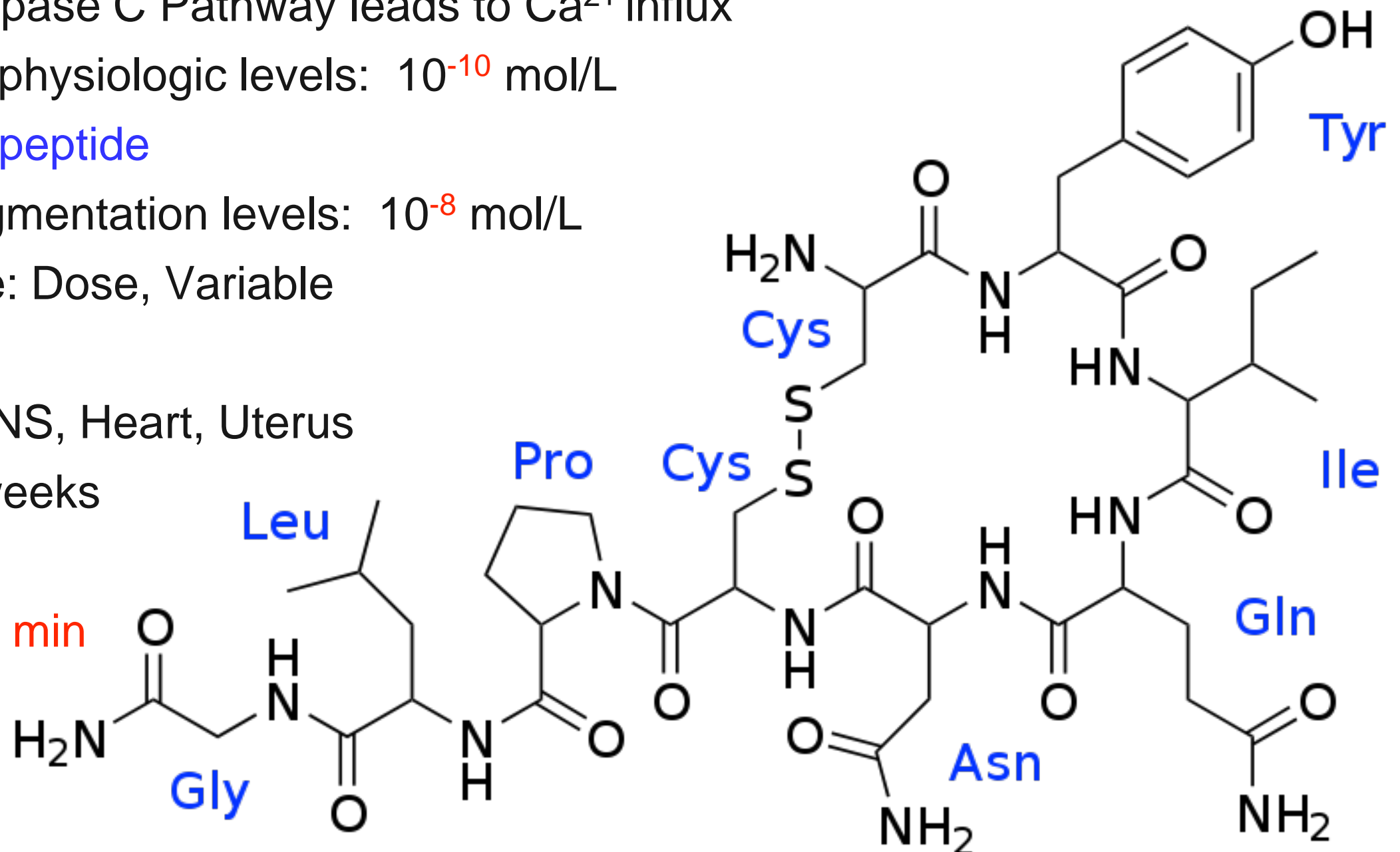
- Labor augmentation levels:  $10^{-8}$  mol/L
- Response: Dose, Variable

## Receptors

- Breast, CNS, Heart, Uterus
- 20 & 30 weeks

## Oxytocinase

- $t_{1/2} = 3$  min





# Oxytocin Receptors

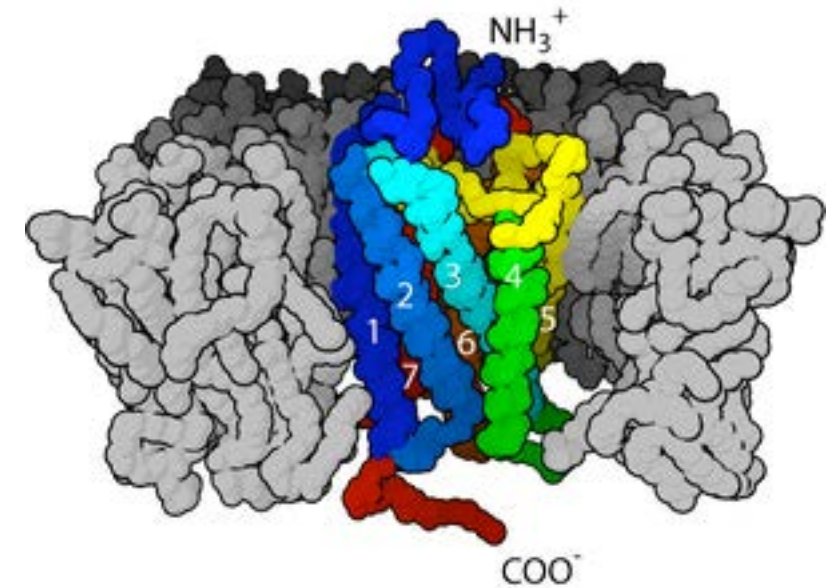
30x increase (8x sensitivity) with gestational age

200x increase in myometrium; numerous fundal, few lower segment and cervical

## 4 Mechanisms for Uterine Contractility

- Inositol Triphosphate (InsP3;  $\text{Ca}^{2+}$ )
- Voltage Gated Depolarization ( $\text{Ca}^{2+}$ )
- Mitogen-activated Protein Kinase (PG)
- Rho-kinase Protein Kinase (PG)

Contraction: Frequency, Amplitude, Duration



Vrachnis N, et al. Int J Endocrinology 2011

Joyce KRS, et al. Reprod Sci 2009;16:501-8

Magalhaes J et al. Reprod Sci 2009;16:510-8

Robinson CR, et al. Am J Obstet Gynecol 2003;188:497-

# Oxytocin Receptors

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**Desensitization** with continuous oxytocin exposure

- Occurs via: Phosphorylation, Internalization, Alteration of mRNA levels
- Lasts for hours to days
- Time and Concentration Dependent

Study	Model	Time	Concentration
Joyce	Rat	1 hrs	$10^{-8}$ mol/L
Robinson	Human	3 hrs	$10^{-8}$ mol/L
Phaneuf	Human	4, 6 hrs	$10^{-8}$ mol/L

Vrachnis N, et al. Int J Endocrinology 2011

Joyce KRS, et al. Reprod Sci 2009;16:501-8

Phaneuf S, et al. Hum Reprod Update 1998;4:625-33

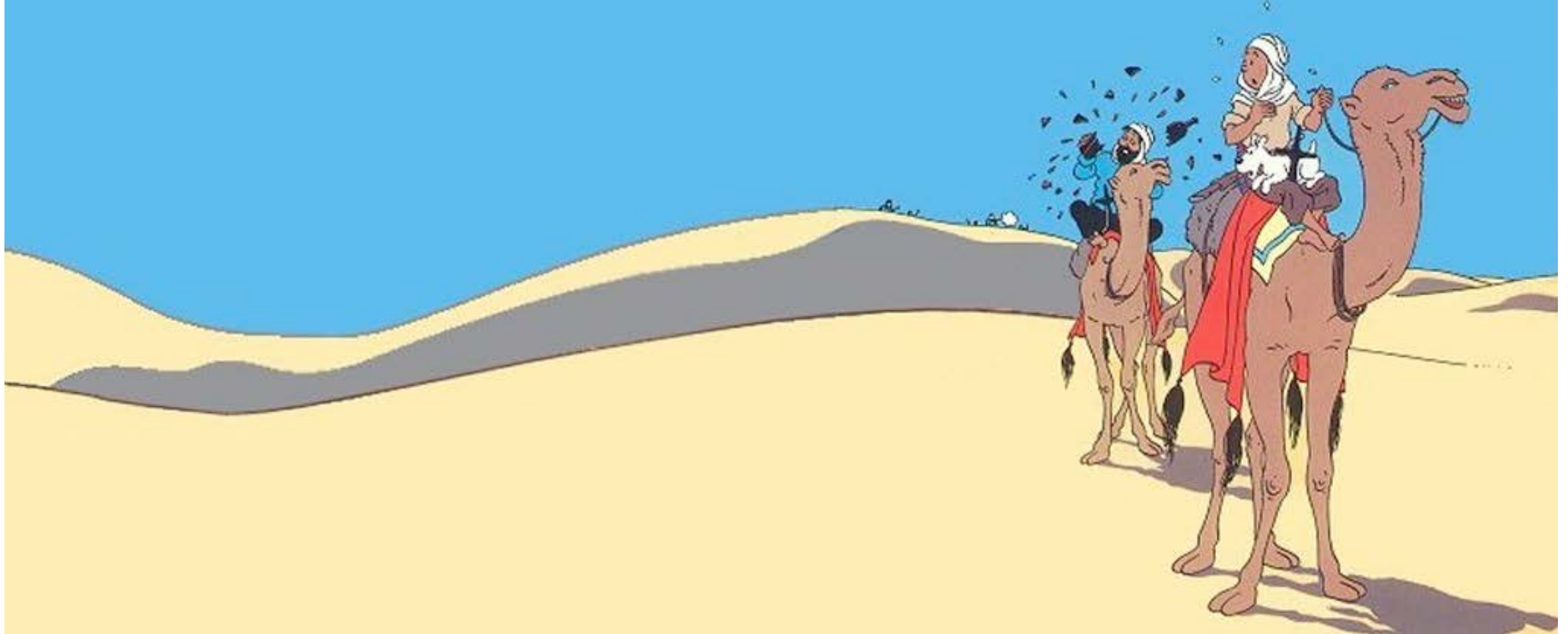
Robinson CR, et al. Am J Obstet Gynecol 2003;188:497-



# Theory: Oxytocin during Cesarean Delivery

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1. Oxytocin is Overdosed
2. This Overdose causes Harm
3. An Alternative Plan is Available



# Oxytocin is Overdosed: Anesthesiologist Guidance

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Chestnut's Obstetric Anesthesia, 5th ed., 2014. Chestnut, Tsen, Wong, Beilin, NganKee, Mhyre

- "...the intravenous use of oxytocin **3 IU** (administered no faster than 15 seconds) at time of infant delivery with reassessment of uterine tone every 3 minutes and the provision of up to **2 additional doses of oxytocin 3 IU**; if inadequate uterine tone still exists, other uterotonic agents should be employed.
- Following the establishment of adequate uterine tone, an infusion of **3 IU/hour** for up to 5 hours has been recommended.

Shnider and Levinson's Anesthesia for Obstetrics, 5th ed, 2012. Suresh, Segal, Preston, Fernando, Mason

- "Oxytocin by infusion (e.g. **20 to 40 units per liter**) should be started as soon as the infant is delivered."



# Oxytocin is Overdosed: Obstetrician Guidance

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**Obstetrics**, 7th ed., 2016. Gabbe, Niebyl, Galan, Jauniaux, Landon, Simpson, Driscoll

- “Control of uterine bleeding is facilitated by oxytocin administration and uterine massage. Oxytocin administration is particularly important following classic cesarean birth.”
- “Control of uterine atony includes uterine massage and medical therapy with **oxytocin 20 to 40 u/L.**”

**Danforth's Obstetric and Gynecology**, 10th ed, 2008. Gibbs, Karlan, Haney, Nygaard

- “**Oxytocin** is added to the patient's intravenous infusion to stimulate uterine contractions and reduce the amount of bleeding.”

**William's Obstetrics**, 25th ed, 2018. Cunningham, Leveno, Bloom, Spong, Dashe

- “**Oxytocin** should be administered to avoid uterine atony”





# Oxytocin is Overdosed: Practice Guidelines

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## American College Ob/Gyn (ACOG)

- “Administer 10-40 IU/L”

## Society Ob/Gyn of Canada (SOGC)

- 5-20 IU IV bolus for vaginal birth
- **Carbetocin** 100 µg IV bolus

## British National Formulary (BNF)

- 5 IU “slow IV” for PPH prevention
- 5-10 IU IV+ infusion for PPH tx
- 5 IU Bolus for Elective CD
  - 86% obstetricians
  - 92% anaesthetists

## Australian/New Zealand obstetricians

- 66% 10 IU; 31% 5 IU

## Oxytocin Guidelines: Empiric and Vague?

British National Formulary, 54th ed. 2007, p 413-6.

ACOG Educational Bulletin No. 243; 1998

SOGC Clinical Practice Guidelines No. 235, 2009

Su LL, et al. Cochrane Syst 2007;3:CD005457

Peters NC, Duvekot JJ. Obstet Gynecol Surv 2009

Wedisinghe L et al. Eur J Obstet Gynecol Reprod Biol 2008;137:27-30

Mockler JC et al. Aust N Z J Obstet Gynecol 2010

# Oxytocin is Overdosed: Practice Guidelines

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## Labor Induction and Augmentation Dose

- Initial dose: 0.5 mIU/min (0.0005 IU/min)
- Max dose: 20 to 30 mIU/min (0.02-0.03 IU/min)

“Start with 0.5  
units of pit,  
with a max  
dose 30 units”

# Oxytocin is Overdosed: Practice Guidelines

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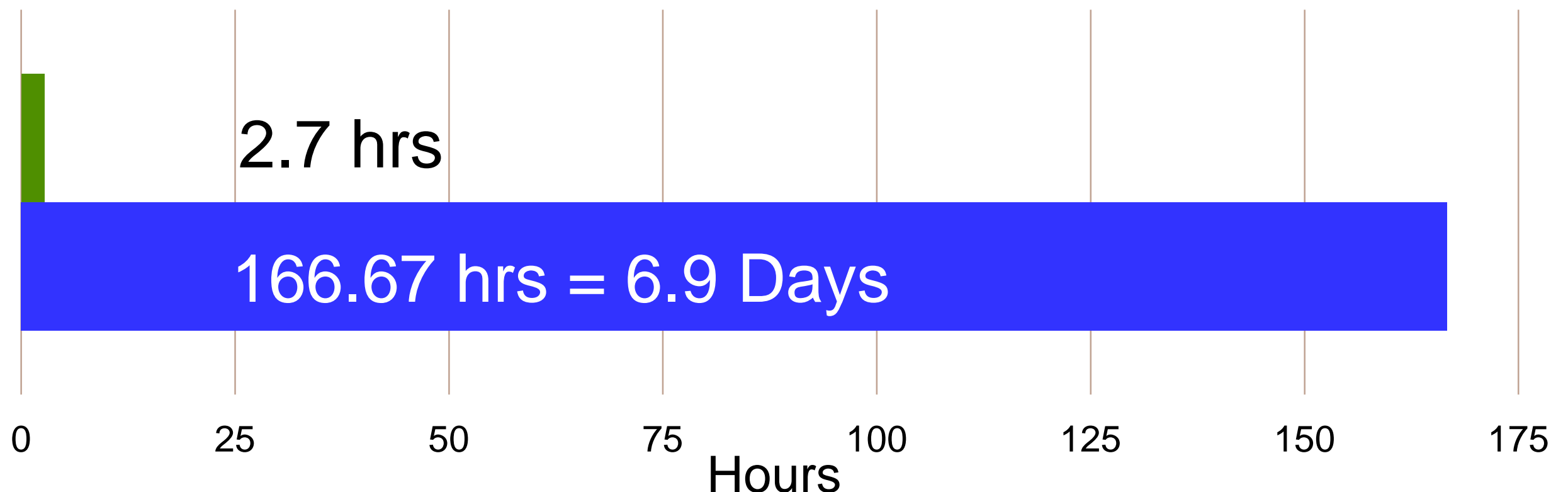
## Labor Induction and Augmentation Dose

- Initial dose: 0.5 mIU/min (0.0005 IU/min)
- Max dose: 20 to 30 mIU/min (0.02-0.03 IU/min)

Time to Reach 5 IU

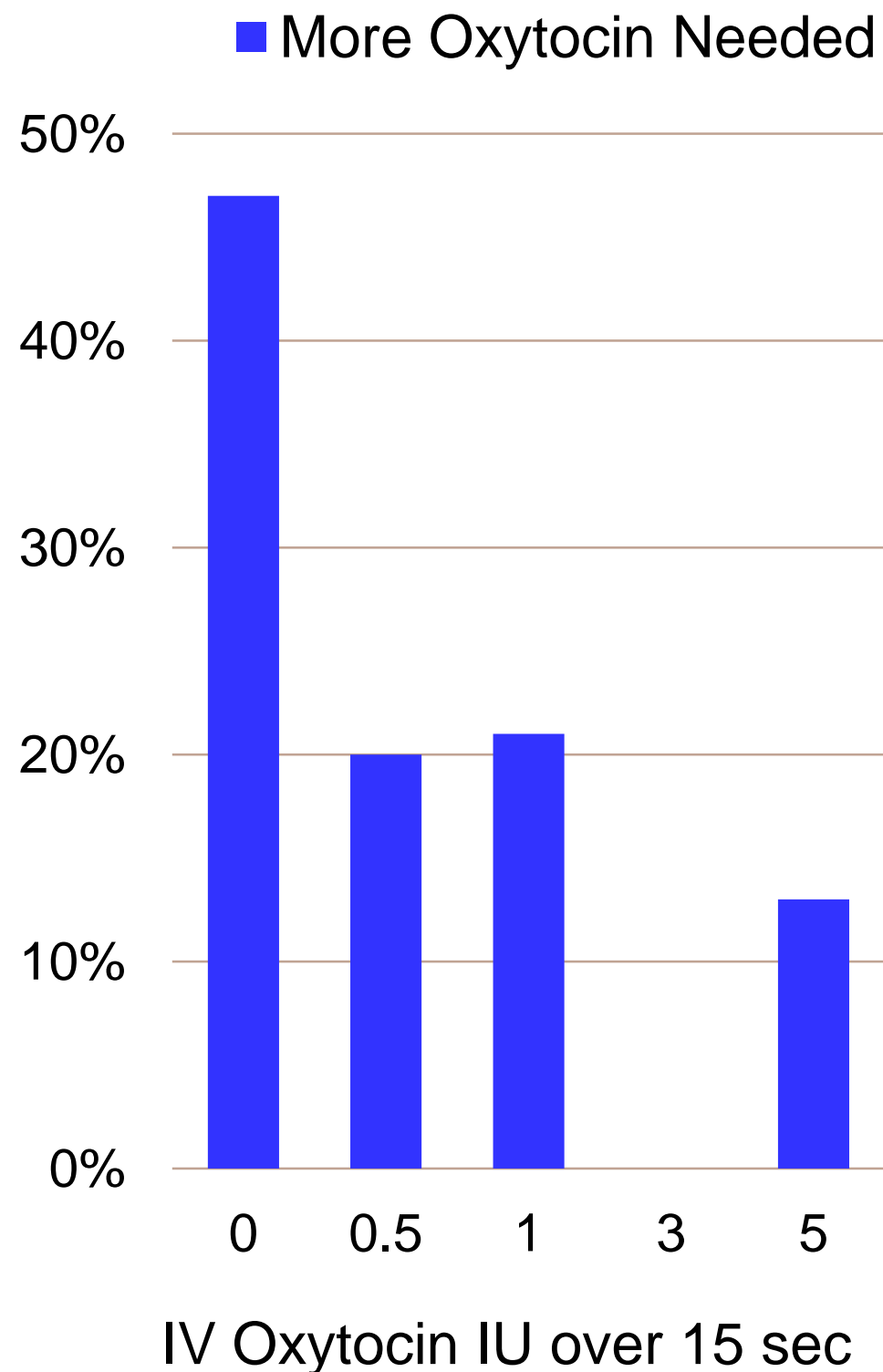
■ Maximum Dose

■ Initial Dose





# Investigation: Oxytocin is Overdosed



## Uterine Tone/Blood Loss Ceiling Effect

- 5 IU = 10, 15, 20 IU
- Dosed 1U/min

## ED<sub>90</sub> Labor Arrest Cesarean

- Oxytocin  $9.8 \pm 6.3$  hrs ( $10.3 \pm 8.2$  mIU/min)
- 0.5 IU/mL initial; up/down increments
- Dosed over 30 secs

- **2.99 IU**

## ED<sub>90</sub> Elective Cesarean

- **0.35 IU**

- Dosed over 30 secs

Sarna MC, et al. Anesth Analg 1997;84:753-6

Carvalho JCA, et al. AJOG 2004;104:1005-1010

Balki M, et al. Ob Gyn 2006;107:45-50

Butwick AJ, et al. BJA 2010; 104:3338-43

# Investigation: Oxytocin causes Harm

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**Clue 1:** THE drug most commonly associated with **preventable adverse events** during childbirth

**Clue 2:** THE drug implicated in almost 50% of **paid obstetric litigation claims**

**Clue 3:** One of just 13 drugs on the list of **high-alert medications** (heightened risk of significant patient harm when used in error).



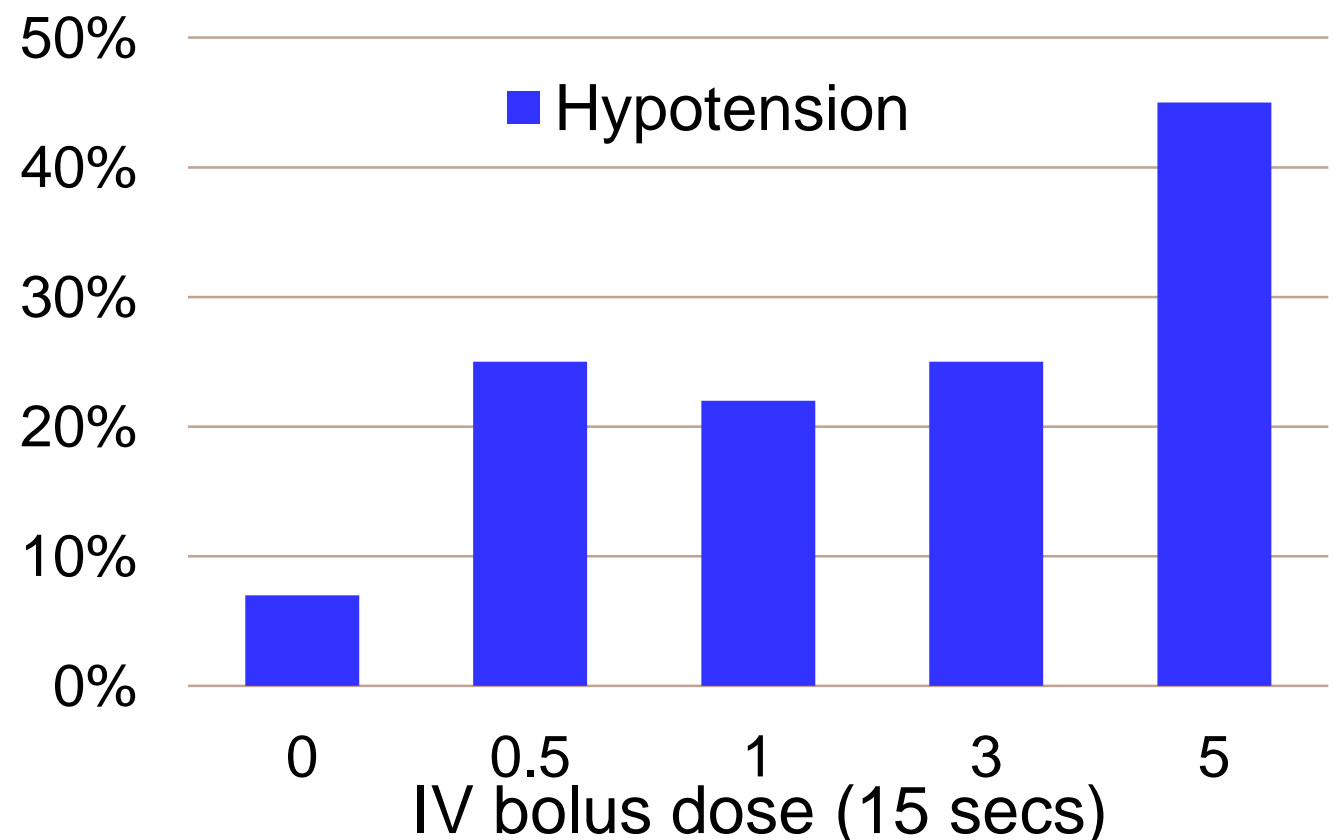
# Investigation: Oxytocin causes Harm

Hypotension Effect	Inotropy (-)	Chronotropy (-)	Vasodilation
<b>Direct:</b> Oxytocin	X	X	
<b>Indirect:</b> Natriuretic/NO	X	X	X
<b>Side:</b> Chlorbutanol	X		X

## Cardiovascular Collapse

- 10 IU Bolus IV

Butwick AJ, et al. BJA 2010; 104:3338-43  
Jankowski M, et al. PNAS 2000;97:6207-11  
Jankowski M, et al. PNAS 1998;95:14558-63  
Gutkowska J, et al. PNAS 1997;94:11704-9  
Rosaeg OP, et al. Anesth Analg 1998;86:40-4  
Thomas TA, Cooper GM. RCOG Press, 2001





# Investigation: Oxytocin causes Harm

## Hypotension

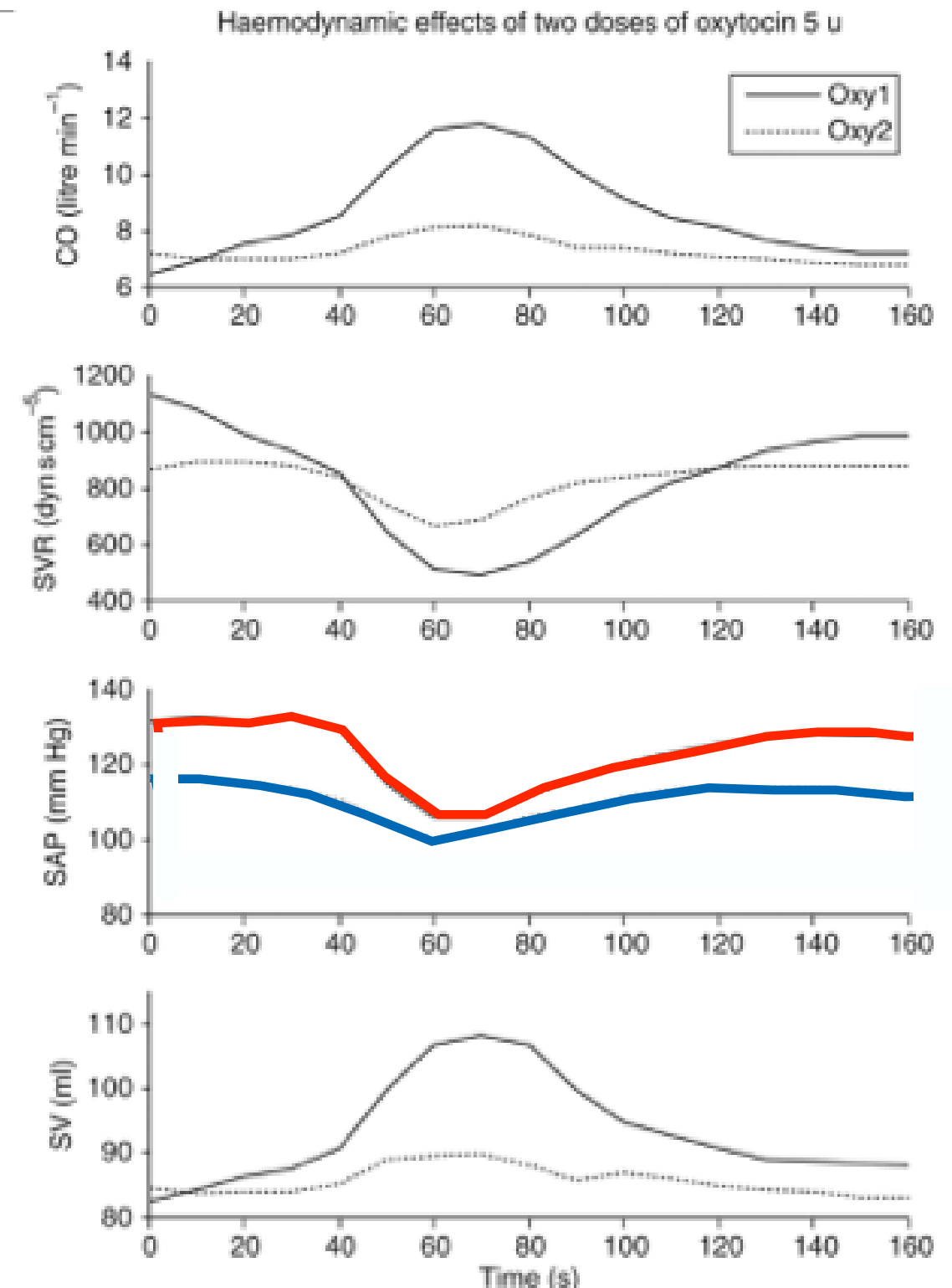
80 women for cesarean

- LidCOPlus (Lithium)  
CO, SV, SVR
- Arterial Line
- Oxytocin 5 IU “injected rapidly”
- SBP decrease **31%** (27-35%)

20 women

- Repeat Oxytocin 5 IU
- Ave 6 min after 1st dose
- SBP decrease **23%** (20-27%)

Langesaeter et al. BJA 2009; 103:260-2



# Investigation: Oxytocin causes Harm

## Hypotension

6 women for cesarean

- Pulse Power Analysis (PulseCO)  
CO, SV, SVR
- Arterial Line
- Oxytocin 5 IU bolus

	Delivery	Oxytocin
MAP (mmHg)	-5.7±15.5	-28.8±8.8
SVR (dynscm)	-27.7±23	-58.5±11.1
CO (L/min)	37.8±27.7	78.5±56
SV (mL)	21.5±25	47.7±20.5
HR (b/min)	14.2±20.1	19.3±26.4

# Investigation: Oxytocin causes Harm

Decreased Free H<sub>2</sub>O Clearance: 0.02 IU/min

- Pulmonary Edema

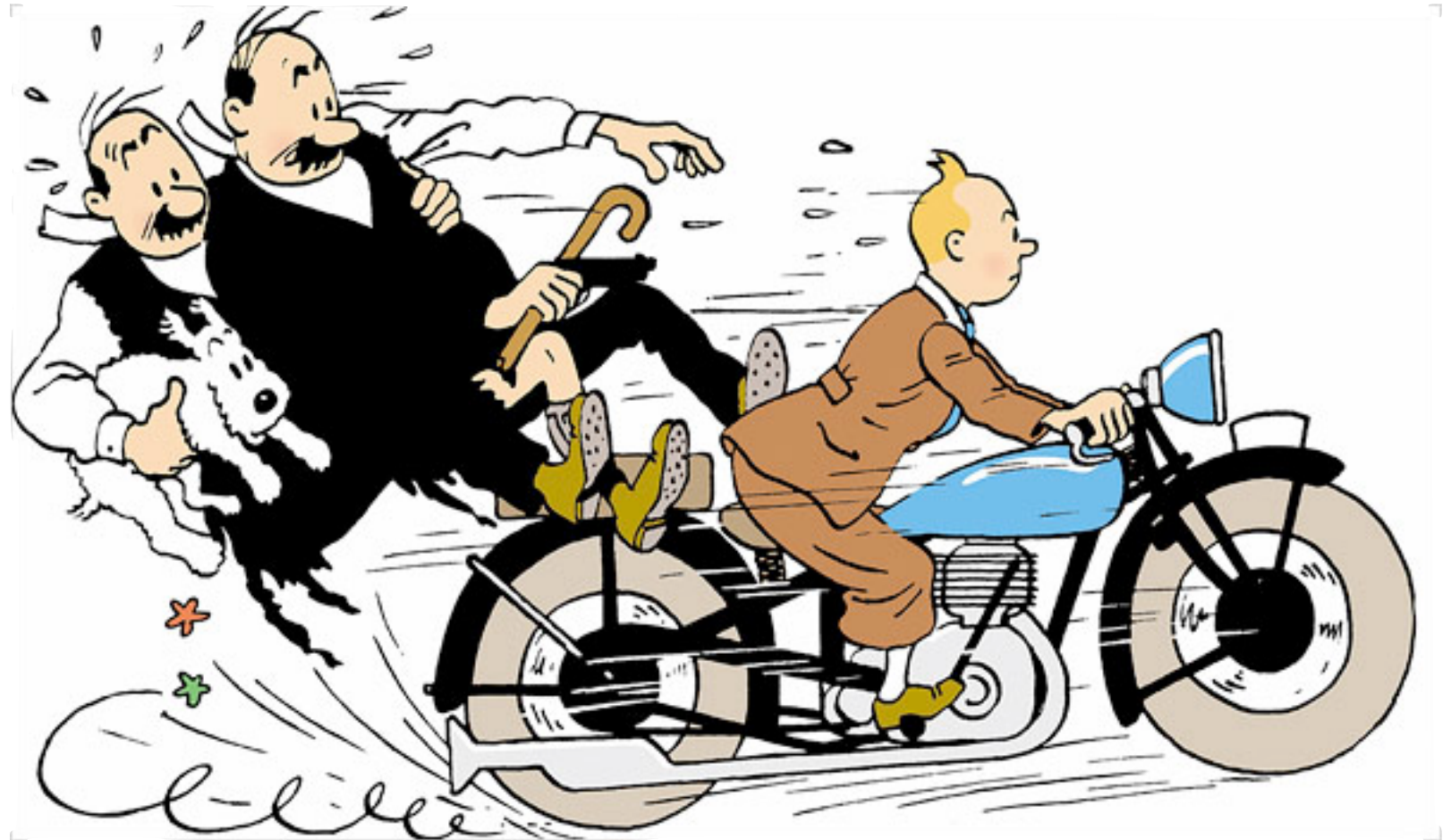
Myocardial Ischemia

- Tachycardia

Complaints

- Flushing: 63%
- Nausea: 38%
- Vomiting: 13%

Uterine Rupture



CEMACH (1997-1999) 2001

Butwick A, et al. Br J Anaesth 2010; 104:338-43

Pinder AJ, et al. IJOA 2002;11:156-9

Sartain JB, et al. Br J Anaesth 2008;101:822-6

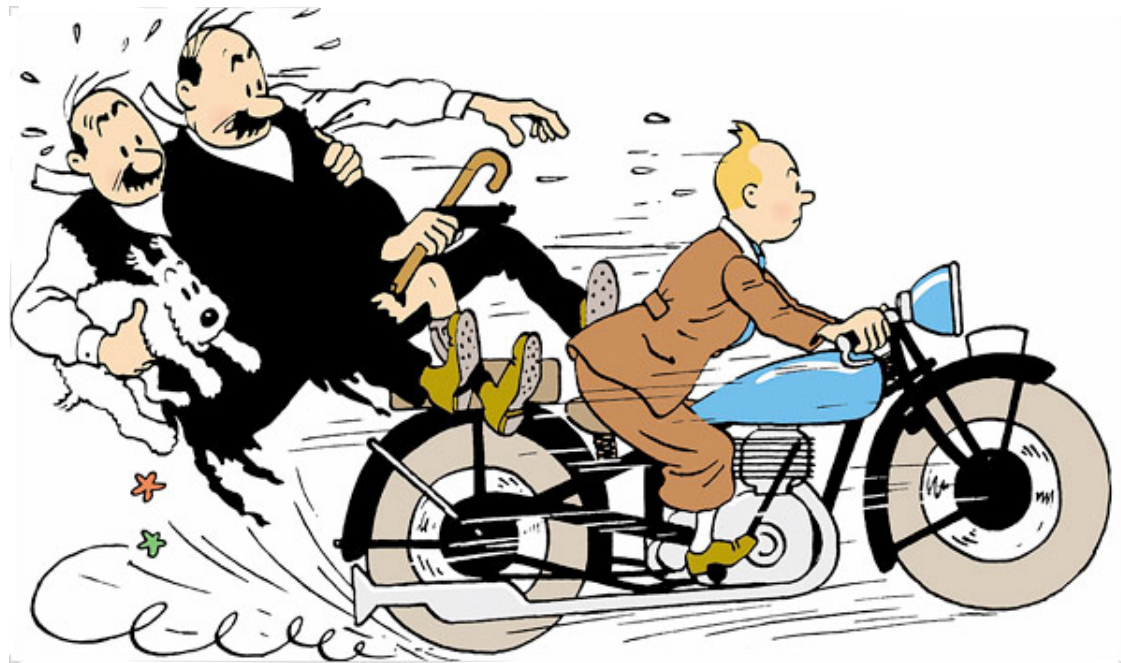
Thomas JS, et al. Br J Anaesth 2007;98:116-9

Archer TL, et al. IJOA 2008;17:247-54

Dyer RA et al. Anesthesiology 2008;108:802-11



# Investigation: Oxytocin causes Harm



## High Postpartum Doses

- Acutely desensitize receptor
- Myometrium less responsive to oxytocin (but not other uterotonics)
- Greater incidence PPH?

## High Intrapartum Doses

- Myometrium less responsive to oxytocin (but not other uterotonics)
- Greater incidence PPH

	PPH	Control	P Value
Oxytocin mU	10,054± 11,340	3,762 ± 7,093	< 0.001
Blood Loss (mL)	1199 ± 785	517± 236	< 0.001
% Hct Change	14.9 ± 4.8	5.8±3.9	< 0.001

Munn MB, et al. Obstet Gynecol 2001;98:386-90  
Balki M, et al. Reprod Sci 2010; 17:269-77  
Dyer R, et al. IJOA 2010;19:313-9  
Tsen LC, Balki M. IJOA 2010;19:243-5  
Grotegut CA, et al. AJOG 2011;204:56.e1-6  
Balki M, Tsen LC. Int Anesth Clinics 2014

# News Flash: An Algorithm for Oxytocin Use

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A Stepwise, Standardized Algorithm

Specific guidance

- Laboring & Non-Laboring Women

## Emphasis

- Avoid Large & Rapid Bolus Doses
- Initial Infusion + Maintenance
- Early Consideration of Alternatives

## Rescue Options

- Methylergonovine Maleate 0.2 mg IM
- Carboprost Tromethamine 0.25 mg IM
- Misoprostol 800 -1000 mcg Rectal



# News Flash: An Algorithm for Oxytocin Use

## “RULE OF THREES”

- 3 IU Oxytocin Load/30 secs
- 3 minute intervals
- 3 total doses (Load + 2 Rescue)
  - 3 IU/hr maintenance (30 IU/L at 100 mL/hr)
- 3 pharmacologic options

## LOADING

- Non-Laboring < 1 IU (ED90 = 0.35 IU)
- Laboring 3 IU (ED90 = 2.99 IU)

## MAINTENANCE 2.4 IU/hr

- 0.04 IU/min (20 IU/L at 120 mL/hr) x 8 hrs
- 0.08 IU/min (40 IU/L at 125 mL/hr)



Tsen LC, Balki M. Int J Obstet Anesth. 2010 Jul;19(3):243-5.

Kovacheva VP, Soens MA, Tsen LC. Anesthesiology 2015;123:92-100

# News Flash: An Algorithm for Uterotonic Use

## OXYTOCIN “RULE OF THREES”

- 3 IU Oxytocin Load/30 secs
- 3 minute intervals
- 3 total doses (Load + 2 Rescue)
- 3 IU/hr maintenance (30 IU/L at 100 mL/hr)
- 3 pharmacologic options

### 1. METHERGINE

- Methylergonovine Maleate 0.2 mg IM
- Ergot Derivative
- Avoid if Hypertension/Eclampsia
- 20 min interval; repeat to 1 mg

### 2. HEMABATE

- Carboprost Tromethamine 0.25 mg IM
- Prostaglandin F2alpha
- Avoid if Asthma?
- 1.5-3.5 hr intervals; total 12 mg, 2 days
- 20 min interval; repeat to 1 mg

### 3. Cytotec

- Misoprostol 800 -1000 mcg Rectal or 600 mcg Buccal
- Prostaglandin E1 Analog
- FDA for NSAID Gastric Ulcer Reduction
- Terminal Half-life 20-40 min

Balki M, et al. Reprod Sci 2010; 17:269-77

Tsen LC, Balki M. IJOA 2010;19:243-5

Balki M, Tsen LC. Int Anesth Clinics 2014





# News Flash: An Algorithm for Uterotonic Use

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## Patterns of Alternative Uterotonic Agents

Premier Database: 2,180,916 Deliveries

Mixed effects, logistic regression

Patient and hospital characteristics

## Frequency

Mean: **7.1%** (IQR 5.2-10.8%)

Range: 1.7% (0.12%) to 25% (1.28%)

**Use not explained by:** patient or hospital characteristics, delivery mode, medical or obstetric conditions, or year

Bateman B, Tsen LC, Liu J, Butwick AJ, Huybrechts KF. Patterns of second-line uterotonic use in large sample of hospitalizations for childbirth in the United States: 2007-2011. *Anesth Analg* 2014 Dec; 119(6):1344-9

## 1. METHERGINE

- Methylergonovine Maleate **0.2 mg** IM
- Ergot Derivative
- Avoid if Hypertension/Eclampsia
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# Uterotonic Agents

Methergine  
0.2 mg IM

Hemebate  
0.25 mg IM

Cytotec  
600 mg B

Oxytocin 3U  
IV Dose over 30 sec

3 min

inadequate

adequate

Oxytocin 3U  
IV Dose over 30 sec

3 min

inadequate

adequate

Oxytocin 3U  
IV Dose over 30 sec

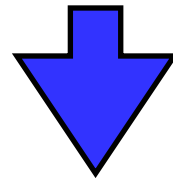
3 min

inadequate

adequate

Oxytocin  
3U/hr  
Infusion

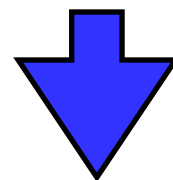
Oxytocin 3U  
IV Dose over 30 sec



Oxytocin 30U  
Saline 1000 mL  
100 mL

Saline 500  
mL  
50 mL

Saline 500  
mL  
37.5 mL



Oxytocin  
3U/hr  
Infusion

# News Flash: An Algorithm for Uterotonic Use

Oxytocin (3IU) + Saline (wide open)

oxytocin 3 IU in 3 mL

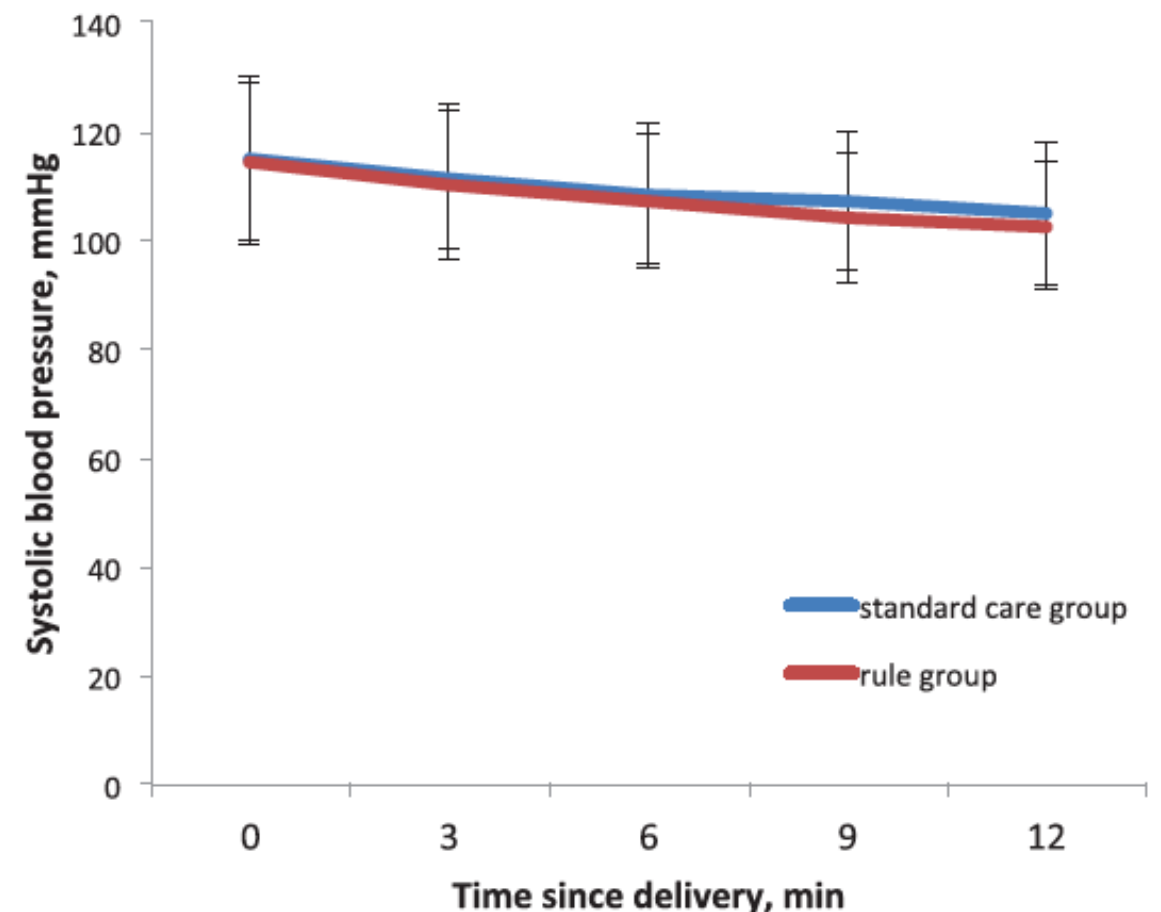
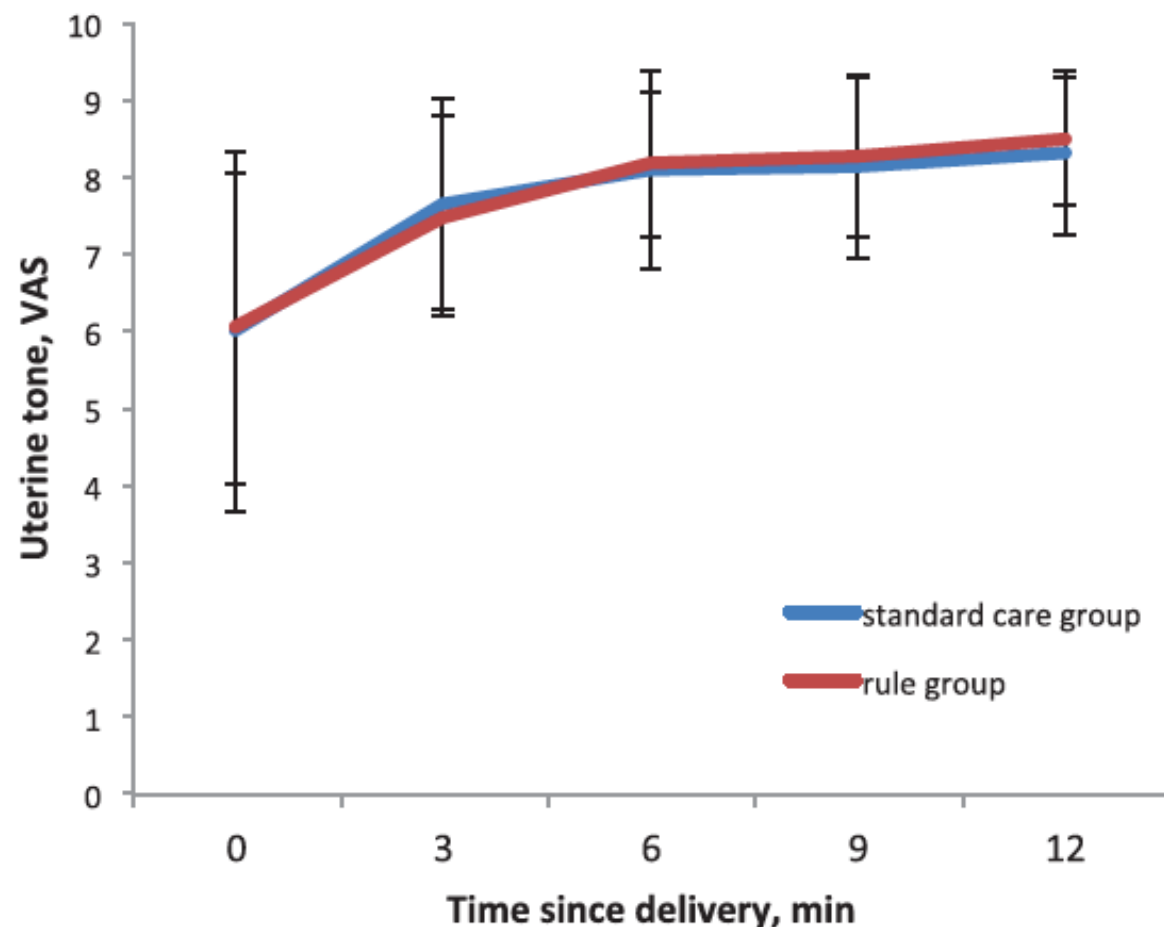
mean, 4.0 IU

Saline (3 mL) + Oxytocin (wide open)

oxytocin 30 IU in 500 mL

mean, 8.4 IU

Uterine Tone at 3, 6, 9, & 12 min





# Summary: Oxytocin

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## THEORY

- Oxytocin is Overdosed?

## INVESTIGATION

- Oxytocin is Overdosed!
- Overdose causes Harm

## NEWS FLASH

- Avoid “rapid IV push” doses
- **Rule of Three's**
- 3 IU doses, 3 min, 3 doses, 3 IU maintenance
- Limit reliance on single agent





Rock: Significant Use of Oxytocin  
Hard Place: Charting a New Course



 **Съезд**  
Congress



5-7 сентября 2018 / Санкт-Петербург  
September 5-7, 2018 / St. Petersburg



Спасибо

вопросов?

