

Concerns about safety of misoprostol with widespread use

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Outline

- Clinical risks
 - Wrong dose, wrong place, wrong time
 - Clinicians' blind faith in misoprostol
 - Toxicity
- Programmatic risks
 - Divert attention and funds from more effective interventions
- Balancing benefits and risk
- Recommendations to minimize risk

East London Hospital Complex

- **Annual workload:**
 - 12 000 births– mainly high-risk referrals
 - >1000 labour inductions
 - 4 000 pregnancy terminations
- Dinoprostone and mifepristone unavailable
- Dependent on misoprostol
- Active in clinical misoprostol research
 - For labour induction we developed the Titrated Oral Misoprostol Solution method to minimize dose and risk
 - For PPH prevention conducted the first randomized trials

Misoprostol Complications

- Because we use so much misoprostol, we also experience complications, mainly related to use for labour induction near term:
 - Uterine hyperstimulation
 - Intrauterine death
 - Uterine rupture

Case 1 of 2008

- Young woman, 2 previous normal births
- Labour induction with low-dose misoprostol (25mcg vaginally then 25mcg orally 2-hourly)
- Spontaneous birth of live baby
- Postpartum haemorrhage, unresponsive to treatment and died 45 min after the birth.

Case 1 of 2008

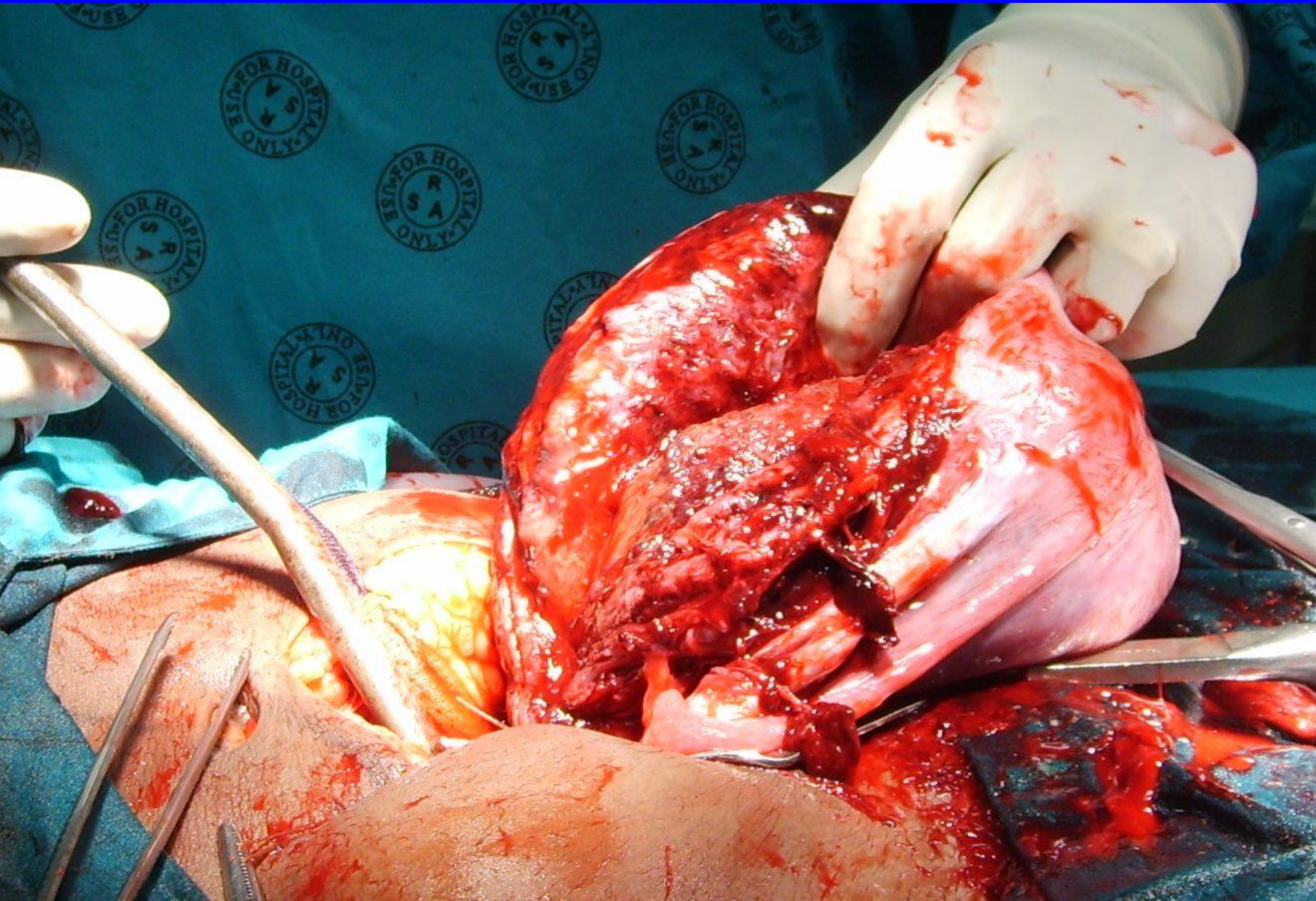
- Young woman Para 2 Gravida 3
- Labour induction with low-dose misoprostol (25mcg vaginally then 25mcg orally 2-hourly)
- Spontaneous birth of live baby
- Postpartum haemorrhage, progressive shock and death 45 min after the birth.

- Post-mortem examination revealed ruptured uterus

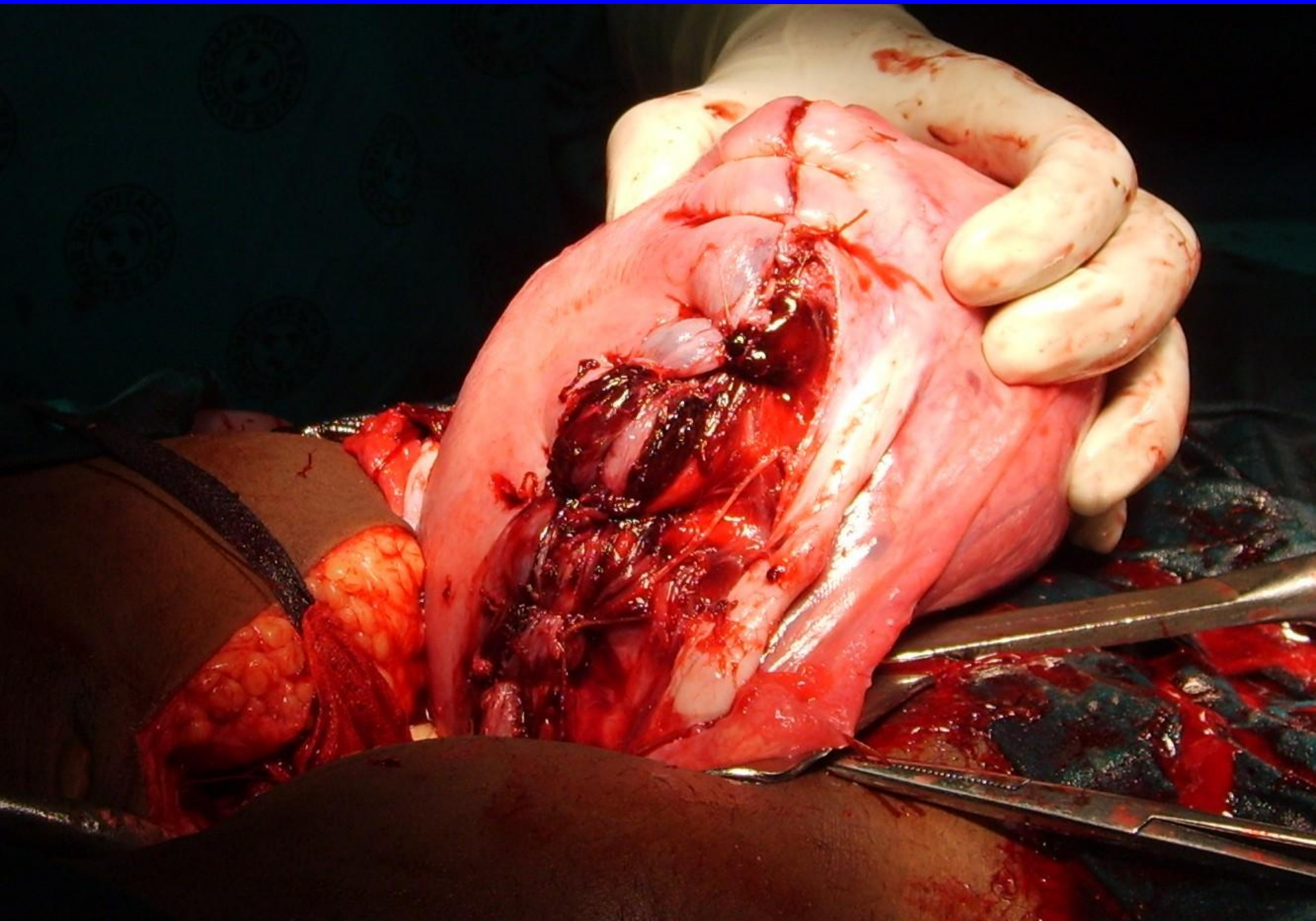
Case 2 of 2008

- 31-year old woman. One previous normal birth
- Labour induction for post-dates pregnancy with low-dose misoprostol 25mcg (1/8 tablet) vaginally one dose only
- 6 hours later noticed to be cold and clammy
- Abdominal palpation: baby felt outside uterus
- Emergency laparotomy: dead baby and placenta in peritoneal cavity

Rupture of posterior uterine wall - repaired



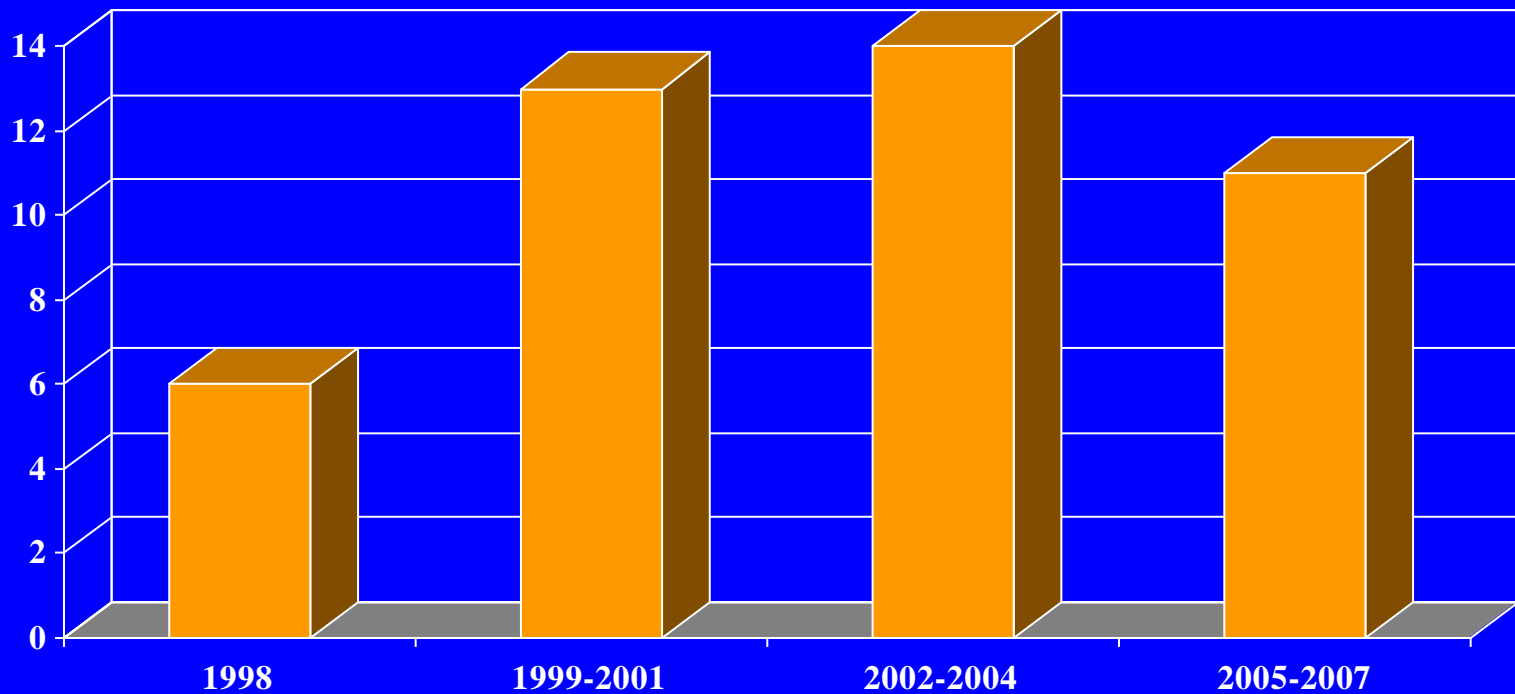
Good recovery postoperatively



Maternal deaths in SA 2005-2007: PPH

Postpartum haemorrhage	383	100%
Retained placenta	88	23%
Atony	67	17.5%
Ruptured uterus with previous c/section	37	9.7%
Ruptured uterus without previous c/section	43	11%
Inverted uterus	7	1.8%
Other genital tract trauma (NB CS)	141	37%

Deaths from rupture of unscarred uterus, as percentage of deaths from haemorrhage (NCCEMD SA)



- The recent epidemic of ruptured uteri is common experience of doctors working in busy obstetric units in poor countries where misoprostol is used



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Balance of benefits and risks

- All effective drugs have side-effects and risks
- No doubt that misoprostol has caused and will continue to cause many deaths of pregnant women and their babies
- We need to be as certain as possible that lives saved will outweigh those lost
- Therefore need to examine effectiveness data very critically

Misoprostol for preventing and treating postpartum haemorrhage: a systematic review of maternal mortality and dose-related effects

Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G; WHO Bull in press

- *Objective* To review randomized trials of misoprostol used for prevention or treatment of postpartum haemorrhage
- Dose-related effects on
 - blood loss
 - pyrexia.
- Maternal deaths

Data collection and analysis

- Randomised trials were checked for eligibility
- Data were extracted and tabulated
- Analysed using Revman 4.3 software

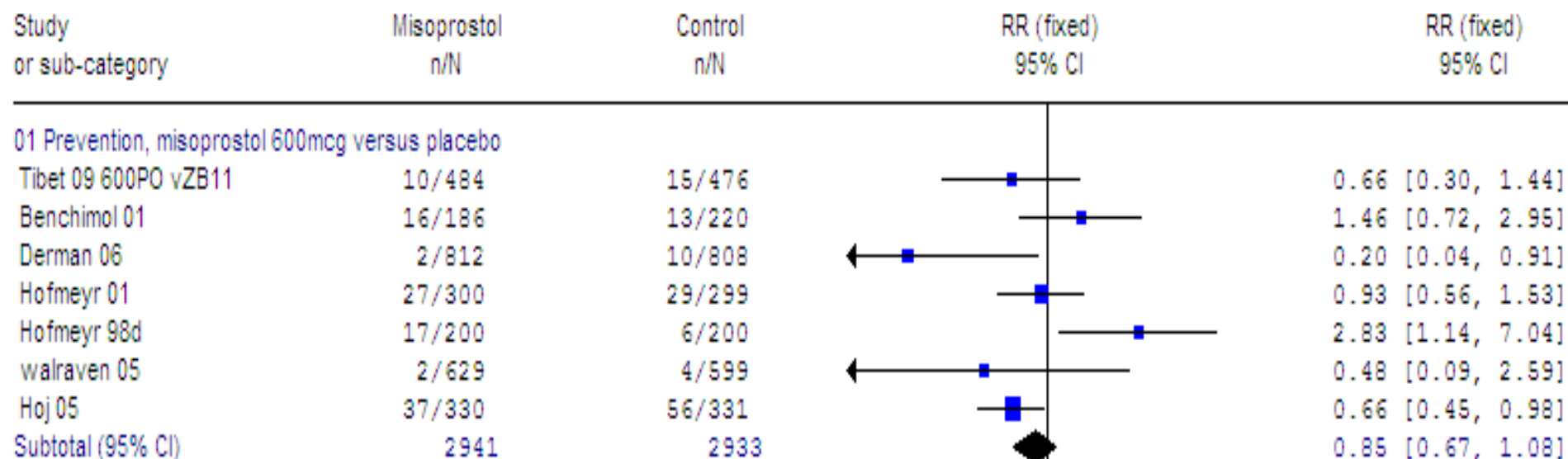
Main results

- Forty-seven trials were included
- More than 40 000 participants

Review: Misoprostol for preventing or treating postpartum haemorrhage (Working copy march09)

Comparison: 01 Misoprostol vs injectable/placebo

Outcome: 03 Blood loss >1000ml

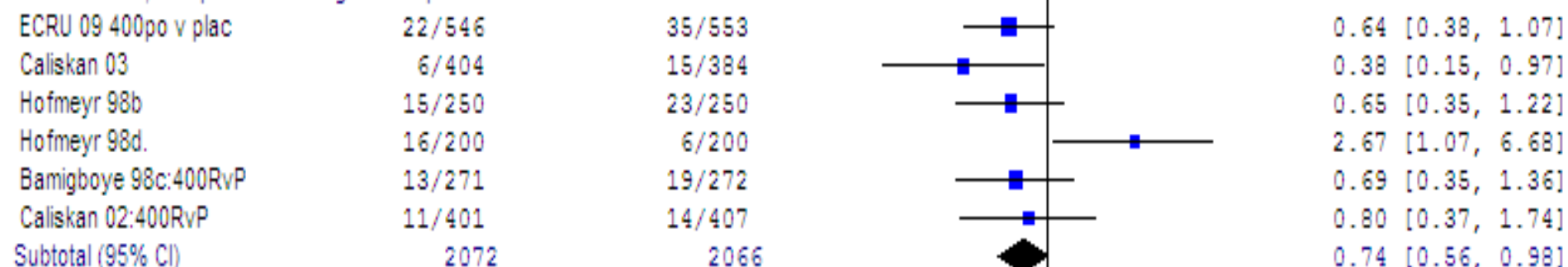


Total events: 111 (Misoprostol), 133 (Control)

Test for heterogeneity: $\text{Chi}^2 = 15.07$, $\text{df} = 6$ ($P = 0.02$), $I^2 = 60.2\%$

Test for overall effect: $Z = 1.33$ ($P = 0.18$)

02 Prevention, misoprostol 400mcg versus placebo



Total events: 83 (Misoprostol), 112 (Control)

Test for heterogeneity: $\text{Chi}^2 = 10.00$, $\text{df} = 5$ ($P = 0.08$), $I^2 = 50.0\%$

Test for overall effect: $Z = 2.12$ ($P = 0.03$)

Misoprostol vs injectable uterotonics: Effect on blood loss >1000ml

04 Prevention, misoprostol 600-800mcg versus other uterotonics

Study	Misoprostol (n/N)	Control (n/N)	Forest Plot	OR [95% CI]
egypt09 800PR v oxy5	17/257	12/257		1.42 [0.69, 2.91]
Belgium 99:600POvU*	1/100	0/100		3.00 [0.12, 72.77]
China 01:600POvU	5/1026	4/1032		1.26 [0.34, 4.67]
France 01 600POvU*	16/186	12/196		1.41 [0.68, 2.89]
India 05a:600POvU*	8/100	6/100		1.33 [0.48, 3.70]
Nigeria 03:600POvU*	0/247	0/249		Not estimable
WHO 01:600POvU	366/9214	263/9228		1.39 [1.19, 1.63]
WHO 99:600POvU	8/199	13/200		0.62 [0.26, 1.46]
India 06f 600PRvU*	0/100	0/100		Not estimable
Ghana 06 800PRvU*	0/225	0/225		Not estimable
Subtotal (95% CI)	11654	11687		1.36 [1.18, 1.57]

Total events: 421 (Misoprostol), 310 (Control)

Test for heterogeneity: $\text{Chi}^2 = 3.60$, $\text{df} = 6$ ($P = 0.73$), $I^2 = 0\%$

Test for overall effect: $Z = 4.21$ ($P < 0.0001$)

05 Prevention, misoprostol 400-500mcg versus other uterotonics

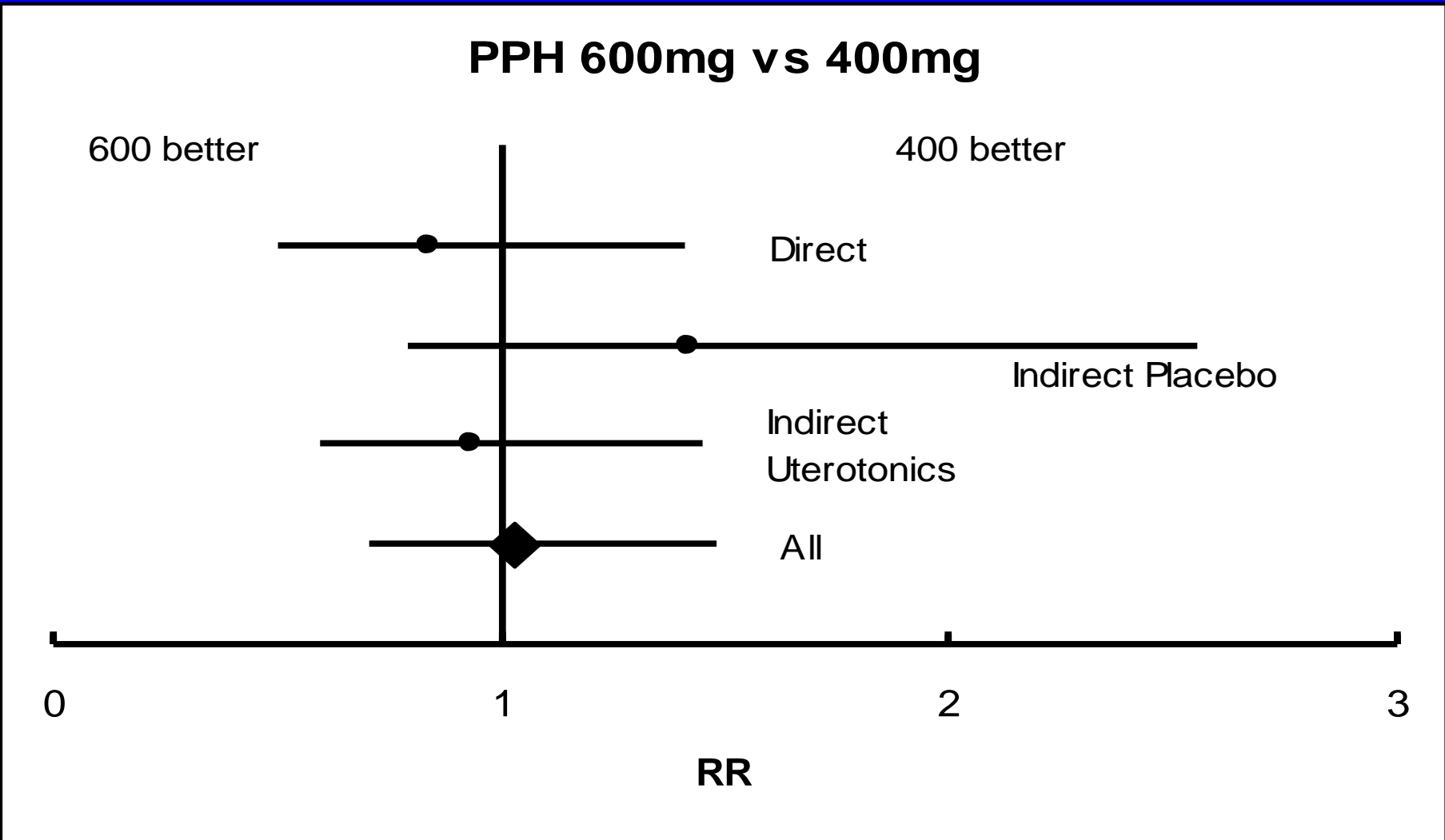
Study	Misoprostol (n/N)	Control (n/N)	Forest Plot	OR [95% CI]
China 07:400POvU*	2/178	1/177		1.99 [0.18, 21.74]
Austral. 99:400POvU*	13/424	7/439		1.92 [0.77, 4.77]
Canada 07:400POvU	14/311	7/311		2.00 [0.82, 4.89]
Ghana 00:400POvU	0/202	0/196		Not estimable
India 06b 400POvU*	1/730	10/1293		0.18 [0.02, 1.38]
Turkey 03:400POvU	14/388	20/782		1.41 [0.72, 2.76]
WHO 99:400POvU	14/198	13/200		1.09 [0.52, 2.25]
Zimbabwe 01:400POvU	9/243	5/256		1.90 [0.64, 5.58]
UK 00:500POvU*	9/501	10/499		0.90 [0.37, 2.19]
UK 01b:500POvU	3/20	3/20		1.00 [0.23, 4.37]
India 04b 400SLvU*	0/60	0/60		Not estimable
India 06a CS400SLvU*	6/50	10/50		0.60 [0.24, 1.53]
Mozambiq. 01:400RvU*	0/323	1/339		0.35 [0.01, 8.56]
Turkey 02:400RvU	17/396	21/809		1.65 [0.88, 3.10]
USA 01:400RvU	15/154	14/161		1.12 [0.56, 2.24]
Subtotal (95% CI)	4178	5592		1.23 [0.96, 1.58]

Total events: 117 (Misoprostol), 122 (Control)

Test for heterogeneity: $\text{Chi}^2 = 10.88$, $\text{df} = 12$ ($P = 0.54$), $I^2 = 0\%$

Test for overall effect: $Z = 1.62$ ($P = 0.11$)

Meta-analysis of direct and adjusted indirect comparisons of misoprostol 600 mcg versus 400 mcg for prevention of postpartum haemorrhage. RR = relative risk. The horizontal bar represents the 95% confidence interval.



Maternal deaths in randomized trials

- Of 11 deaths reported, 8 occurred in women receiving misoprostol vs 3 in the control groups; all 8 received 600mcg or more
- Including the unpublished data referred to yesterday, of 14 deaths to date, 10 occurred in the misoprostol groups vs 4 in the control groups

Maternal deaths in randomized trials

	Misoprostol (all 600mcg or more)	Control	
Misoprostol vs Oxytocin	3	3	NS
Misoprostol vs Placebo	7	1	NS

Use of misoprostol to reduce maternal deaths is intuitively logical

PPH is a common cause of maternal death

Misoprostol reduces blood loss

Misoprostol should reduce deaths

An increase in deaths with misoprostol seems implausible

Use of misoprostol to reduce maternal deaths is intuitively logical

PPH is a common cause of maternal death	Ventricular arrhythmia is a common cause of death after myocardial infarction
Misoprostol reduces blood loss	Class 1 antiarrhythmics reduce ventricular arrhythmias
Misoprostol should reduce deaths	Class 1 antiarrhythmics should reduce deaths
An increase in deaths with misoprostol seems implausible	

Use of misoprostol to reduce maternal deaths is intuitively logical

PPH is a common cause of maternal death	Ventricular arrhythmia is a common cause of death after myocardial infarction
Misoprostol reduces blood loss	Class 1 antiarrhythmics reduce ventricular arrhythmias
Misoprostol should reduce deaths	Class 1 antiarrhythmics should reduce deaths
An increase in deaths with misoprostol seems implausible	Cardiac Arrhythmia Suppression Trial (CAST) : deaths after 1 year: Antiarrhythmics: 10% Placebo: 5% (Epstein AE, et al. JAMA 1993; 270:2451-5)
??	Estimated antiarrhythmics killed >10 000 people

What other effects of misoprostol do we know about?

- Ubiquitous effects on many organ systems, eg:
- Impaired platelet function
 - (Beales IL, Clemons M, Kong WM. Misoprostol-associated platelet aggregation dysfunction and increased gastrointestinal blood loss. Eur J Gastroenterol Hepatol. 1997 Jan;9(1):91-2)
- Prostaglandins have complex effects on blood vessels – may cause vasodilation or vasoconstriction. Misoprostol 400mcg causes increased peripheral resistance. Larger doses?
- (Brecht T. Effects of misoprostol on human circulation. Prostaglandins. 1987;33 Suppl:51-60)
- Etc.

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Recommendations to minimize risk

- Change focus of global efforts from misoprostol-centered to PPH prevention-centered
- Redouble efforts to make oxytocin available to all (more effective and safer than misoprostol)
- Grand Challenge for basic research into non-injectable administration of oxytocin, ergometrine or other uterotonic
- As Part of current efforts to disseminate misoprostol, include a huge cluster randomized trial:
 - Study regions: misoprostol introduction
 - Comparison regions: oxytocin promotion
 - Outcome: Regional overall maternal mortality
- Until there is evidence that 600mcg is more effective than 400mcg, recommend initial dose not exceeding 400mcg





Photo: Nic Stavakis