Prevention and treatment of postpartum haemorrhage

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Training in Reproductive Health Research
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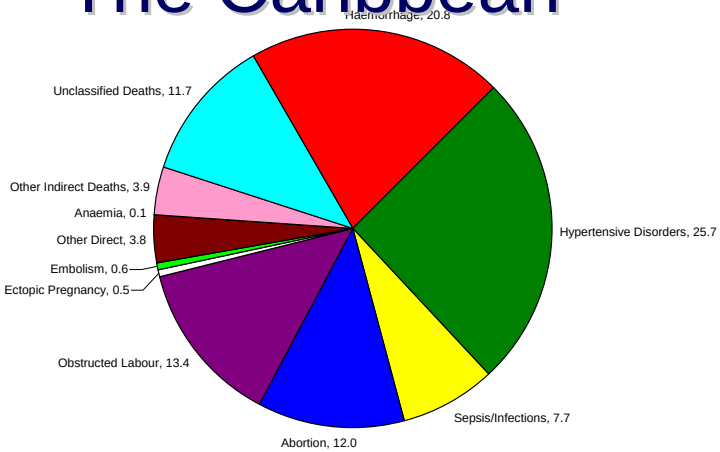
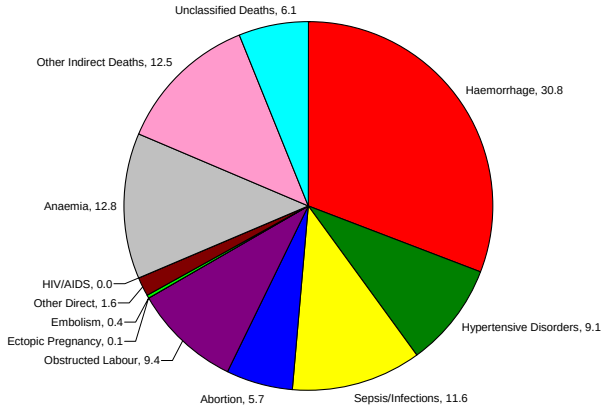
Latin America & The Caribbean



Asia



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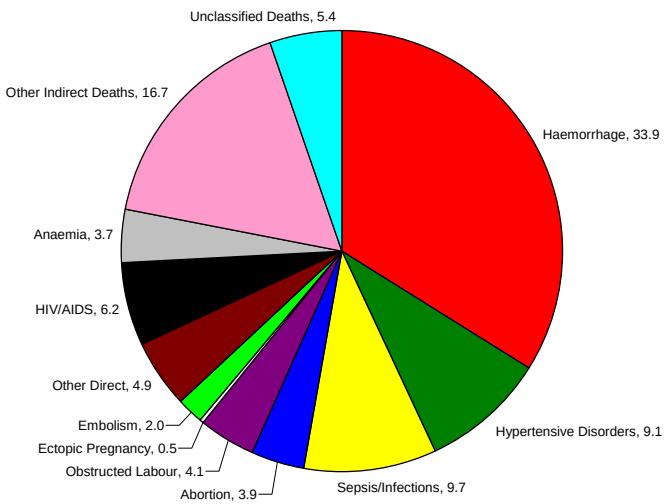
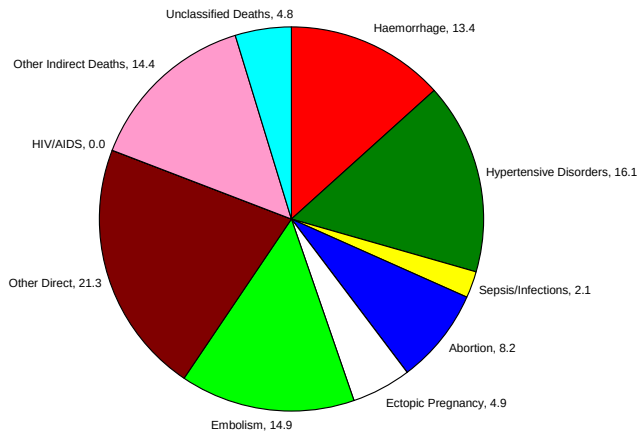


Developed Countries



PPH (controlled trials - bleeding >500 ml)

Study	Years	Country	Quality	N of women with PPH	Total N of women	Prevalence
Khan 1997	1995-1995	UAE	Medium	90	821	10.96
Nordstrom 1997	1993-1994	Sweden	Low	74	487	15.20
Waldenstrom 1997a	1989-1993	Sweden	Low	106	847	12.51
Waldenstrom 1997b	1989-1993	Sweden	Low	106	834	12.71
Rogers 1998	1993-1995	UK	Medium	126	764	16.49
Rotchell 1998	1992-1994	Barbados	Low	175	1822	9.60
Walley 2000	1998-1999	Ghana	Low	2	401	0.50
Kundodyiwa 2001	1999-2000	Zimbabwe	High	34	256	13.30

Strategies to reduce postpartum blood loss

- Active management
  - which uterotonic?
- Restrictive episiotomy
- Retained placenta management

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What is active management?

- Early cord clamping
- Uterotonic
- Controlled cord traction

- Uterine massage
- Variations of each of the components common

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01 Active vs expectant management (all women)				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 PPH clinically estimated blood loss greater than or equal to 500mls	4	6284	Relative Risk [Fixed] [95% CI]	0.38 [0.32, 0.46]
02 Severe PPH clinically estimated blood loss greater than or equal to 1000mls	4	6284	Relative Risk [Fixed] [95% CI]	0.33 [0.21, 0.51]
03 Mean blood loss (mls)	2	2941	WMD [Fixed] [95% CI]	-79.327 [-94.288, -64.367]
04 Maternal Hb < 9 g/dl 24 - 48 hours post partum	4	4255	Relative Risk [Fixed] [95% CI]	0.40 [0.29, 0.55]
05 Blood transfusion	5	6477	Relative Risk [Fixed] [95% CI]	0.34 [0.22, 0.53]
06 Iron tablets during the puerperium	1	1447	Relative Risk [Fixed] [95% CI]	0.60 [0.49, 0.74]
07 Therapeutic oxytocics	5	6477	Relative Risk [Fixed] [95% CI]	0.20 [0.17, 0.25]
08 Third stage > 20 minutes	3	4637	Relative Risk [Fixed] [95% CI]	0.15 [0.12, 0.19]
09 Third stage > 40 minutes	3	4636	Relative Risk [Fixed] [95% CI]	0.18 [0.14, 0.24]
10 Mean length of third stage (minutes)	3	4589	WMD [Fixed] [95% CI]	-9.766 [-10.004, -9.529]
11 Manual removal of placenta	5	6477	Relative Risk [Fixed] [95% CI]	1.21 [0.82, 1.78]
12 Subsequent surgical evacuation of retained products of conception	3	4636	Relative Risk [Fixed] [95% CI]	0.74 [0.43, 1.28]
13 Diastolic blood pressure > 100 mmHg between delivery of baby and discharge from labour ward	3	4636	Relative Risk [Fixed] [95% CI]	3.46 [1.68, 7.09]
14 Vomiting between delivery of baby and discharge from labour ward	3	3407	Relative Risk [Fixed] [95% CI]	2.19 [1.68, 2.86]
15 Nausea between delivery of baby and discharge from labour ward	3	3407	Relative Risk [Fixed] [95% CI]	1.83 [1.51, 2.23]
16 Headache between delivery of baby and discharge from labour ward	3	3405	Relative Risk [Fixed] [95% CI]	1.97 [1.01, 3.82]
17 Maternal pain during third stage of labour	2	391	Relative Risk [Fixed] [95% CI]	1.01 [0.55, 1.86]
18 Maternal dissatisfaction with third stage management	1	1466	Relative Risk [Fixed] [95% CI]	0.56 [0.35, 0.90]

Oxytocin vs. syntometrine

01 syntometrine vs oxytocin (any dose)				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 blood loss >500 ml	6	10091	Peto OR [95% CI]	0.74 [0.65, 0.85]
02 blood loss > 1000ml	4	6963	Peto OR [95% CI]	0.79 [0.59, 1.06]
03 manual removal of the placenta	5	8341	Peto OR [95% CI]	1.04 [0.80, 1.34]
04 blood transfusion	3	6502	Peto OR [95% CI]	1.25 [0.77, 2.05]
05 elevation diastolic blood pressure	3	6495	Peto OR [95% CI]	2.81 [1.67, 4.74]
06 vomiting	3	6495	Peto OR [95% CI]	4.86 [3.99, 5.92]
07 apgar score <6 @ 5 min.	2	5511	Peto OR [95% CI]	1.01 [0.67, 1.51]
08 jaundice	2	5511	Peto OR [95% CI]	0.98 [0.85, 1.13]
09 not breastfed at discharge	1	3483	Peto OR [95% CI]	1.10 [0.91, 1.33]
02 syntometrine vs oxytocin (5iu)				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 blood loss >500 ml	3	3089	Peto OR [95% CI]	0.36 [0.23, 0.55]
02 blood loss > 1000ml	1	461	Peto OR [95% CI]	0.14 [0.00, 6.85]
03 manual removal of the placenta	2	1839	Peto OR [95% CI]	1.54 [0.81, 2.92]
04 blood transfusion			No numerical data	
05 elevation of diastolic blood pressure			No numerical data	
06 vomiting			No numerical data	
07 apgar score <6 @ 5 min.			No numerical data	
08 jaundice			No numerical data	
09 not breastfed at discharge			No numerical data	
03 syntometrine vs oxytocin (10iu)				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 blood loss >500 ml	4	8002	Peto OR [95% CI]	0.81 [0.70, 0.94]
02 blood loss > 1000ml	3	6502	Peto OR [95% CI]	0.80 [0.60, 1.07]
03 manual removal of the placenta	3	6502	Peto OR [95% CI]	0.96 [0.73, 1.27]
04 blood transfusion	3	6502	Peto OR [95% CI]	1.25 [0.77, 2.05]
05 elevation of diastolic blood pressure	3	6495	Peto OR [95% CI]	2.81 [1.67, 4.74]
06 vomiting	3	6495	Peto OR [95% CI]	4.86 [3.99, 5.92]
07 apgar < 6 @ 5 min	2	5511	Peto OR [95% CI]	1.00 [0.67, 1.50]
08 jaundice	2	5511	Peto OR [95% CI]	0.98 [0.85, 1.13]
09 not breastfed at discharge	1	3483	Peto OR [95% CI]	1.10 [0.91, 1.33]

WHO multicentre randomised trial of misoprostol in the management of the third stage of labour

*A Metin Gülmezoglu, José Villar, Nguyen Thi Nhu Ngoc, Gilda Piaggio, Guillermo Carroli, Lekan Adetoro, Hany Abdel-Aleem, Linan Cheng, G Justus Hofmeyr, Pisake Lumbiganon, Christian Unger, Walter Prendiville, Alain Pinol, Diana Elbourne, Hazem El-Refaey, Kenneth F Schulz, for the WHO Collaborative Group To Evaluate Misoprostol in the Management of the Third Stage of Labour**

Summary

Background Postpartum haemorrhage is a leading cause of maternal morbidity and mortality. Active management of the third stage of labour, including use of a uterotonic agent, has been shown to reduce blood loss. Misoprostol (a prostaglandin E1 analogue) has been suggested for this purpose because it has strong uterotonic effects, can be given orally, is inexpensive, and does not need refrigeration for storage. We did a multicentre, double-blind, randomised controlled trial to determine whether oral misoprostol is as effective as oxytocin during the third stage of labour.

Methods In hospitals in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam, we randomly assigned women about to deliver vaginally to receive 600 μg misoprostol orally or 10 IU oxytocin intravenously or intramuscularly, according to routine practice, plus corresponding identical placebos. The medications were administered immediately after delivery as part of the active management of the third stage of labour. The primary outcomes were measured postpartum blood loss of 1000 mL or more, and the use of additional uterotonics without an unacceptable level of side-effects. We chose an upper limit of a 35% increase in the risk of blood loss of 1000 mL or more as the margin of clinical equivalence, which was assessed by the confidence interval of the relative risk. Analysis was by intention to treat.

Findings 9264 women were assigned misoprostol and 9266 oxytocin. 37 women in the misoprostol group and 34 in the oxytocin group had emergency caesarean sections and were excluded. 366 (4%) of women on misoprostol had a measured blood loss of 1000 mL or more, compared with 263 (3%) of those on oxytocin (relative risk 1·39 [95% CI 1·19–1·63], p<0·0001). 1398 (15%) women in the misoprostol group and 1002 (11%) in the oxytocin group required additional uterotonics (1·40 [1·29–1·51], p<0·0001). Misoprostol use was also associated with a significantly higher incidence of shivering (3·48 [3·15–3·84]) and raised body temperature (7·17 [5·67–9·07]) in the first hour after delivery.

Interpretation 10 IU oxytocin (intravenous or intramuscular) is preferable to 600 μg oral misoprostol in the active management of the third stage of labour in hospital settings where active management is the norm.

Lancet 2001; **358:** 689–95
See Commentary page 682

Primary outcomes

- Measured blood loss ≥ 1000 mls.
- Additional uterotonic

- Secondary outcomes
  - Measured blood loss ≥ 500 mls.
  - Blood transfusion
  - Manual removal of the placenta
  - Late haemorrhage (after 1st hour)
  - Treatments for severe haemorrhage (hysterectomy, bimanual compression, etc.)

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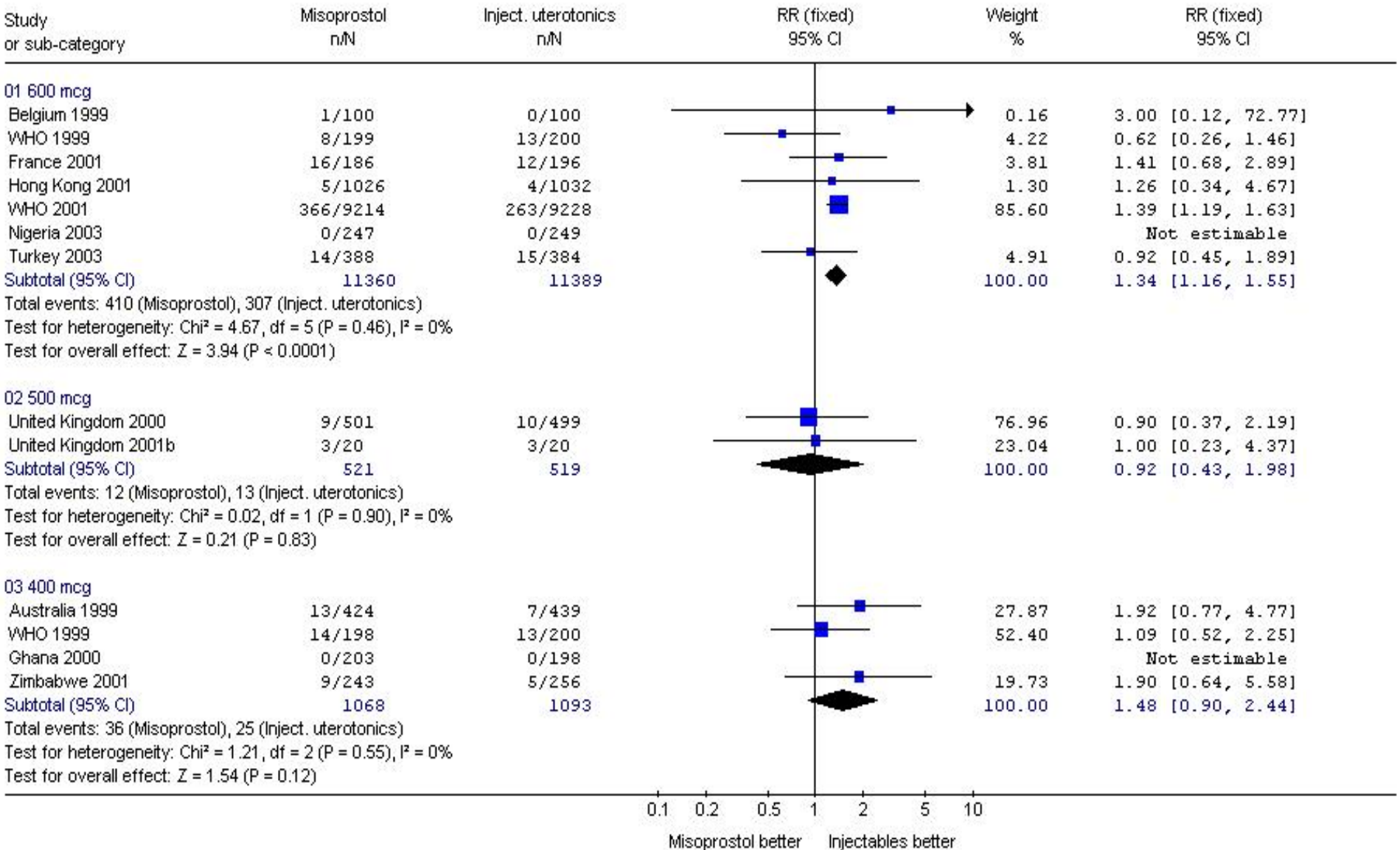
Primary outcomes
Relative Risk

	Misoprostol n=9225 %	Oxytocin n=9228 %	RR	95% CI
Blood loss ≥ 1000 mls*	4.0	2.9	1.39	1.19 to 1.63
Additional uterotonics	15.2	10.9	1.40	1.29 to 1.51

*=9214

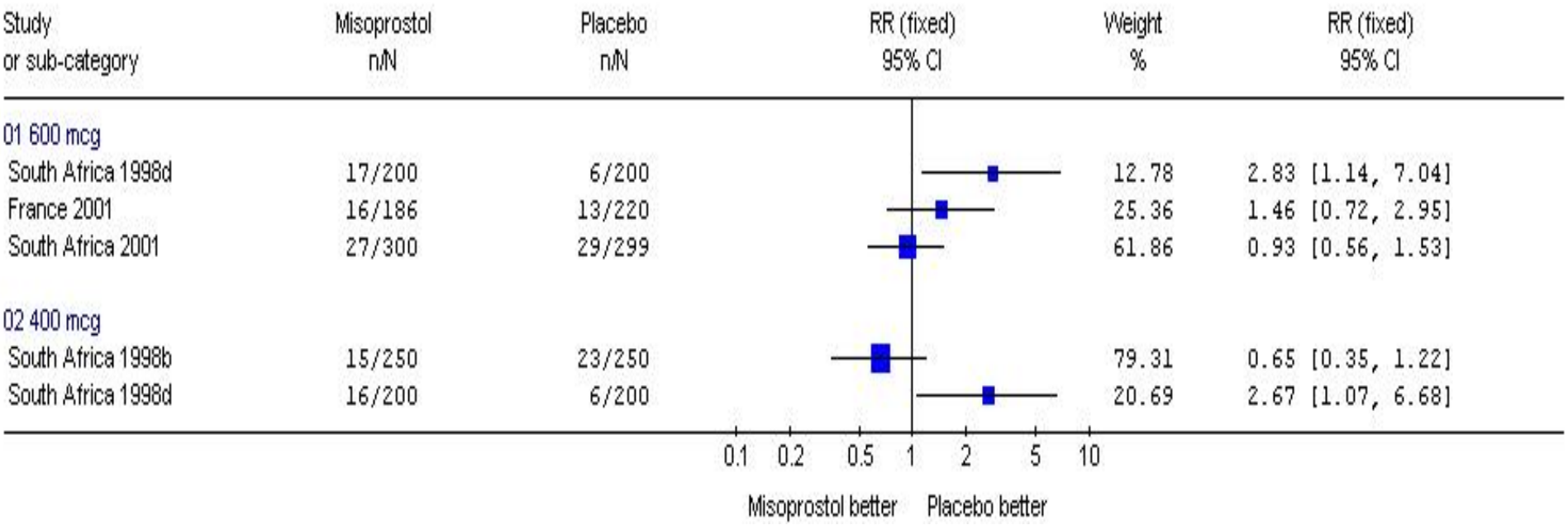
Misoprostol vs conventional injectable uterotonics

Review: Prostaglandins for prevention of postpartum haemorrhage
Comparison: 02 Oral misoprostol versus injectable uterotonics
Outcome: 02 Severe postpartum haemorrhage (>= 1000 ml)



Misoprostol vs placebo

Review: Prostaglandins for prevention of postpartum haemorrhage
Comparison: 01 Oral misoprostol versus no uterotonic/placebo
Outcome: 02 Severe postpartum haemorrhage (>= 1000 ml)



Restricted episiotomy

06 Severe vaginal/perineal trauma (primiparae)	3	2331	Relative Risk [Fixed] [95% CI]	1.15 [0.84, 1.58]
07 Severe vaginal/perineal trauma (multiparae)	3	1973	Relative Risk [Fixed] [95% CI]	1.14 [0.52, 2.48]
08 Severe perineal trauma	5	3850	Relative Risk [Fixed] [95% CI]	0.80 [0.55, 1.16]
09 Severe perineal trauma (primiparae)	5	2390	Relative Risk [Fixed] [95% CI]	0.84 [0.56, 1.25]
10 Severe perineal trauma (multiparae)	3	1460	Relative Risk [Fixed] [95% CI]	0.71 [0.28, 1.82]
11 Any posterior perineal trauma	4	2079	Relative Risk [Fixed] [95% CI]	0.88 [0.84, 0.92]
12 Any posterior perineal trauma (primiparae)	4	1157	Relative Risk [Fixed] [95% CI]	0.86 [0.82, 0.91]
13 Any posterior perineal trauma (multiparae)	2	922	Relative Risk [Fixed] [95% CI]	0.91 [0.83, 0.99]
14 Any anterior trauma	4	4342	Relative Risk [Fixed] [95% CI]	1.79 [1.55, 2.07]
15 Any anterior trauma (primiparae)	3	976	Relative Risk [Fixed] [95% CI]	1.24 [0.96, 1.60]
16 Any anterior trauma (multiparae)	2	922	Relative Risk [Fixed] [95% CI]	1.61 [1.19, 2.18]
17 Need for suturing perineal trauma	5	4133	Relative Risk [Fixed] [95% CI]	0.74 [0.71, 0.77]
18 Need for suturing perineal trauma (primiparae)	5	2441	Relative Risk [Fixed] [95% CI]	0.73 [0.70, 0.76]
19 Need for suturing perineal trauma (multiparae)	3	1692	Relative Risk [Fixed] [95% CI]	0.78 [0.72, 0.83]
20 Estimated blood loss at delivery	1	165	WMD [Fixed] [95% CI]	-58.000 [-107.575, -8.425]
21 Moderate/severe perineal pain at 3 days	1	165	Relative Risk [Fixed] [95% CI]	0.71 [0.48, 1.05]
22 Any perineal pain at discharge	1	2422	Relative Risk [Fixed] [95% CI]	0.72 [0.65, 0.81]
23 Any perineal pain at 10 days	1	885	Relative Risk [Fixed] [95% CI]	1.00 [0.78, 1.27]

Umbilical vein injection for retained placenta

02 SALINE SOLUTION PLUS OXYTOCIN VERSUS EXPECTANT MANAGEMENT				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Manual removal of the placenta	5	454	Relative Risk [Fixed] [95% CI]	0.86 [0.72, 1.01]
02 Postpartum haemorrhage	1	55	Relative Risk [Fixed] [95% CI]	1.12 [0.07, 16.95]
03 Blood loss = or > 500 ml after entry	1	130	Relative Risk [Fixed] [95% CI]	1.53 [0.88, 2.67]
04 Blood loss = or > 1000 ml after entry	1	130	Relative Risk [Fixed] [95% CI]	1.29 [0.38, 4.34]
05 Haemoglobin 24-48 hours postpartum	1	164	WMD [Fixed] [95% CI]	0.000 [-0.614, 0.614]
06 Haemoglobin 40-45 days postpartum	1	96	WMD [Fixed] [95% CI]	0.500 [-0.142, 1.142]
07 Blood transfusion	2	237	Relative Risk [Fixed] [95% CI]	0.89 [0.50, 1.58]
08 Curettage	1	182	Relative Risk [Fixed] [95% CI]	0.69 [0.44, 1.09]
09 Infection	1	179	Relative Risk [Fixed] [95% CI]	1.16 [0.32, 4.16]
10 Stay at hospital more than two days	1	180	Relative Risk [Fixed] [95% CI]	1.09 [0.60, 1.97]
03 SALINE SOLUTION PLUS OXYTOCIN VERSUS SALINE SOLUTION				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Manual removal of the placenta	10	649	Relative Risk [Fixed] [95% CI]	0.79 [0.69, 0.92]
02 Length of third stage of labour	1	30	WMD [Fixed] [95% CI]	16.200 [-15.223, 47.623]
03 Blood loss	2	48	WMD [Fixed] [95% CI]	21.605 [-49.728, 92.938]
04 Postpartum haemorrhage	1	52	Relative Risk [Fixed] [95% CI]	3.00 [0.13, 70.42]
05 Blood loss = or > 500 ml after entry	1	130	Relative Risk [Fixed] [95% CI]	1.43 [0.83, 2.45]
06 Blood loss = or > 1000 ml after entry	1	130	Relative Risk [Fixed] [95% CI]	1.71 [0.45, 6.56]
07 Haemoglobin 24-48 hours pospartum	1	167	WMD [Fixed] [95% CI]	-0.100 [-0.758, 0.558]
08 Haemoglobin 40-45 days postpartum	1	91	WMD [Fixed] [95% CI]	0.100 [-0.578, 0.778]
09 Blood transfusion	2	238	Relative Risk [Fixed]	1.17 [0.63, 2.19]

Summary

- Active management reduces blood loss
- Choice between oxytocin (10IU) and syntometrine involves trade-offs
- Routine episiotomy should be abandoned
- Retained placenta should be managed actively
  - Oxytocin +saline infusion is likely to reduce the likelihood of manual removal of the placenta

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Management of postpartum haemorrhage

- Essential components
  - treat shock
  - ascertain the origin of bleeding and treat accordingly
    - control lower tract bleeding
    - ensure uterine contraction
    - remove placenta

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Nonsurgical emergency measures

- Uterine massage
- Uterotonics
  - ergometrine IV, oxytocin infusion (20-40 IU)
  - PGF2alpha IM or intramyometrial, intrauterine gemeprost pessaries
  - misoprostol
- Compression of aorta against the sacral promontory
- Bimanual uterine compression
- Stretching the uterine arteries by elevating the uterus
- Intrauterine balloon, condom

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Nonsurgical emergency measures

- Intrauterine pressure
  - Packing
  - Sengstaken-Blakemore tube
  - Foley catheter with a large bulb
  - Silicone water-filled balloon

- *Uterine artery embolization*

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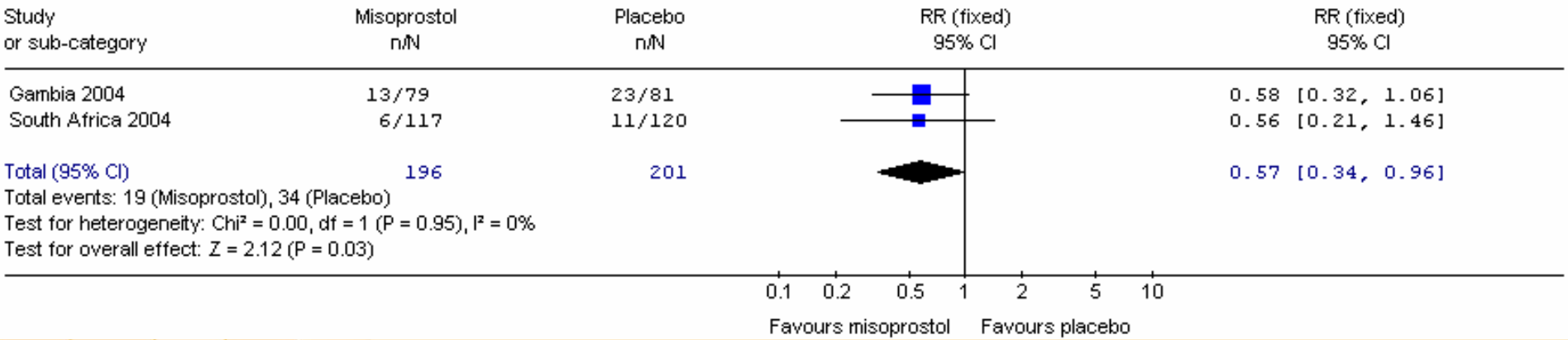
Misoprostol

- 3 trials (two in S.Africa, one in The Gambia)
- Promising but the effects on substantive outcomes unclear

The effect of misoprostol on measured blood loss of 500 ml or more after enrolment

Review: Misoprostol for treatment of postpartum haemorrhage
Comparison: 01 Misoprostol versus placebo
Outcome: 01 Blood loss 500ml or more

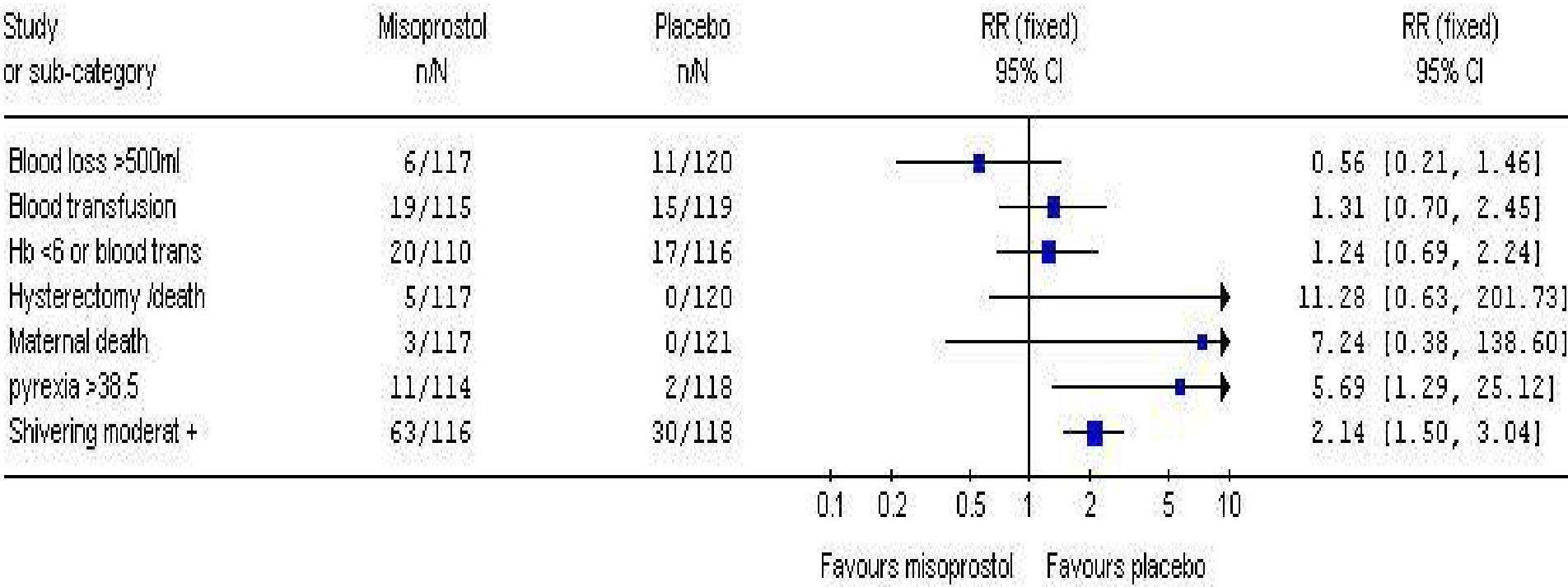


Misoprostol for Rx of PPH: Methods:

- East London Hospital Complex, Tembisa and Chris Hani Baragwanath Hospitals
- Routine active management of the third stage
- Women with more than usual postpartum bleeding invited to participate, and to sign informed consent
- All routine treatment given from a special 'Postpartum Haemorrhage Trolley'
- In addition, drew the next in a series of randomised treatment packs containing either misoprostol 5 X 200μg or identical looking placebo
- Given 1 orally, 2 sublingually and 2 rectally.

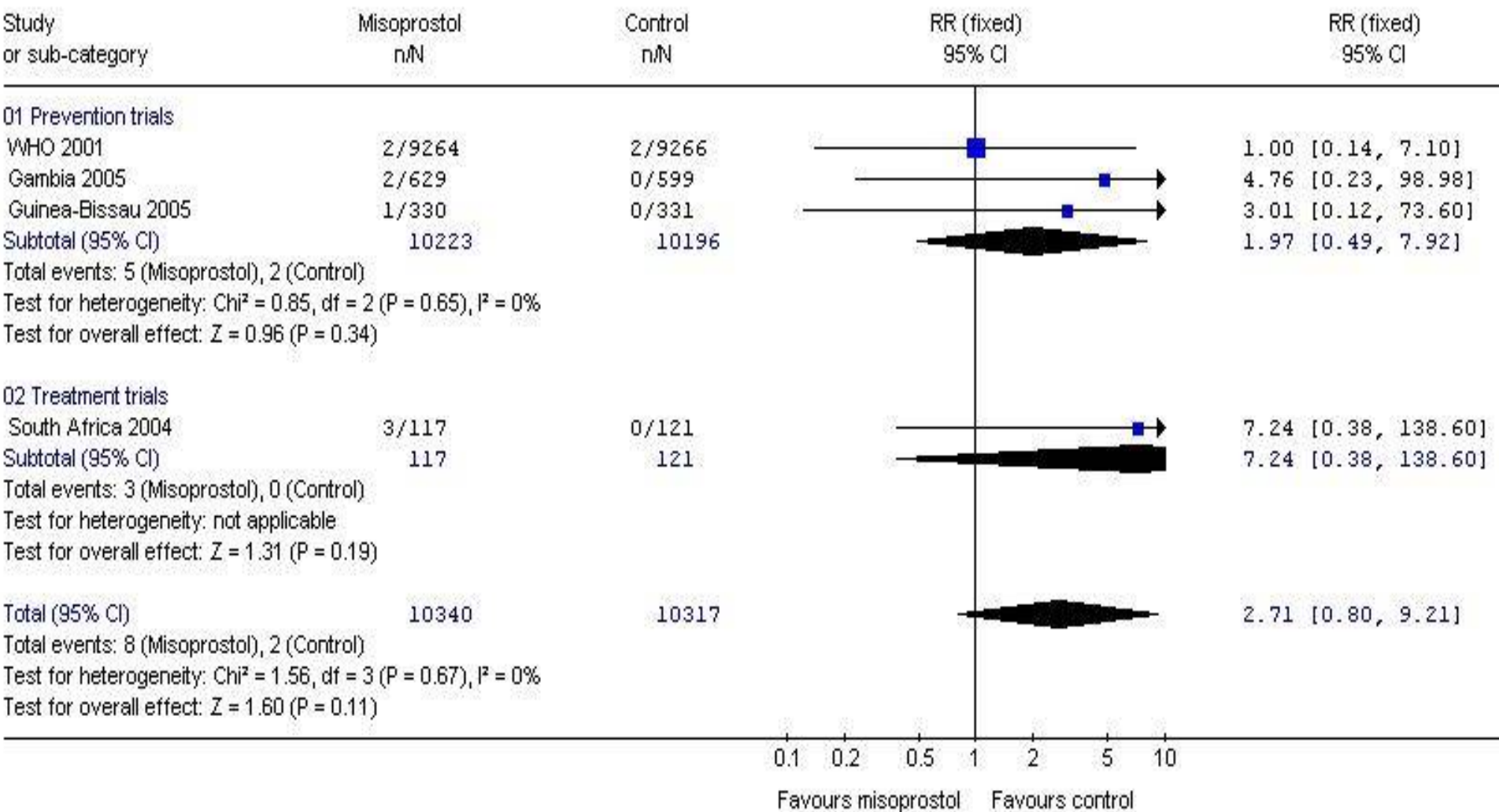
Results: Misoprostol vs placebo

Review: Misoprostol for treatment of postpartum haemorrhage (ECRU study)
Comparison: 02 Misoprostol versus placebo
Outcome: 10 Categorical outcomes



Review: all misoprostol in 3rd stage trials with maternal deaths

Review: Misoprostol in labour 3rd stage
Comparison: 01 Misoprostol vs injectable/placebo
Outcome: 01 Maternal death



Surgical measures

- Exploration under g/a
- Removal of retained products of conception
- Internal iliac artery ligation
- Stepwise uterine and ovarian artery ligation
- Vaginal uterine artery ligation
- Uterine repair or hysterectomy
- Full-thickness uterine suture

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Summary

- Misoprostol is promising but should be evaluated in well-conducted trials with appropriate power.
- Other methods have not been evaluated rigorously.

Assessment of blood loss after delivery

- Definition (500, 1000 ml)
- Visual estimation
  - Underestimates blood loss
  - More with increased blood loss
- Measurement
  - Several methods exist with varying precision and practicality
  - WHO protocol for measurement of blood loss used in the Misoprostol Trial

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