WHO Guidance:
2nd edition revised *Managing Complications in Pregnancy and Childbirth (MCPC)* and Redesign of WHO Guideline Derivative Tools

An Unfinished Agenda in Maternal Health: Meeting the Needs of Women with Preeclampsia/Eclampsia and Postpartum Hemorrhage

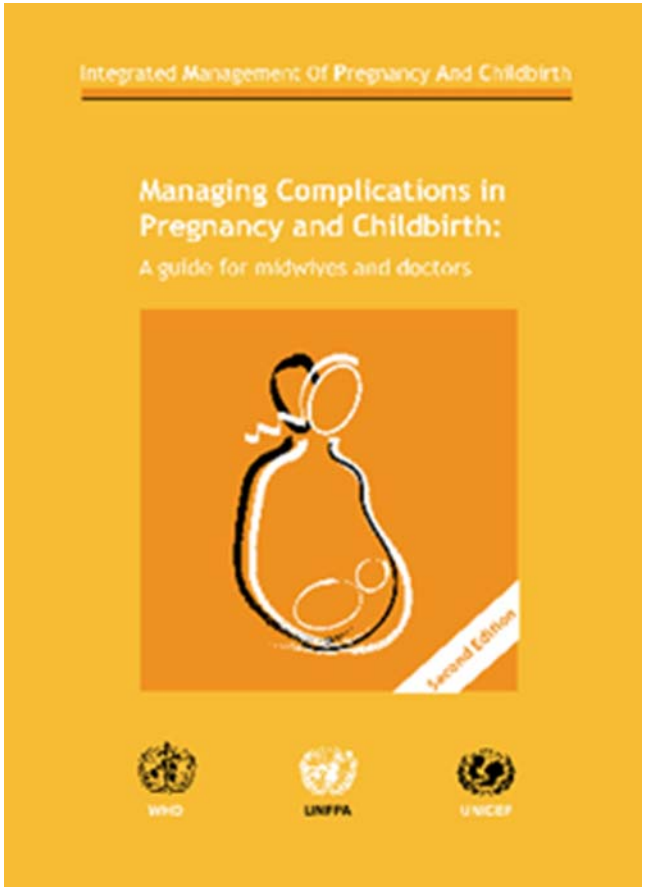
Washington, DC
June 13, 2017

Outline

- MCPC background and revision process
- MCPC PE/E and PPH updates
- Redesign of WHO IMPAC derivative tools: initial discussions

MCPC Background

- Reference manual for midwives and doctors working at district hospital level in low resource settings.
- Uses symptom-sign based step-by-step approach (e.g. vaginal bleeding in early pregnancy).
  - Section 1: Clinical principles
  - Section 2: Symptoms
  - Section 3: Procedures
  - Section 4: Appendix.
- The first edition published in 2000 (re-printed 2007)



Revision Process

- **User Survey** conducted in **2015** to solicit feedback from key stakeholders to inform revisions of MCPC
- Core team of **WHO, partners and external experts** prioritized **18 chapters for revision**
- **WHO and MCSP** members assigned as **technical co-leads** for each chapter
- Revisions had to be consistent with **previously updated WHO guidelines and recommendations**
- **WHO Guideline Review Committee (GRC)** requirements: external review conducted by **2 expert external reviewers** for each revised chapter

18 Revised MCPC Priority Chapters

Chapter Category	Chapters Revised
Clinical Principles (Section 1)	• Emotional and psychological support • Emergencies • General care principles • Antibiotic therapy • Operative care principles • Normal labour and childbirth • Newborn care principles
Symptoms (Section 2)	• Vaginal bleeding in early pregnancy • Vaginal bleeding after childbirth • Elevated blood pressure, headache, blurred vision, convulsions or loss of consciousness • Fever during pregnancy and labour • Fever after childbirth • Difficulty in breathing • Prelabour rupture of membranes • Immediate newborn conditions or problem
Procedures (Section 3)	• Induction and augmentation of labour • Manual removal of placenta • Repair of vaginal and perineal tears

PE/E: Key Areas of Revision

- **Revised classification** framework for Hypertensive Disorders of Pregnancy
- **Prevention** of PE/E
  - Calcium supplementation
  - Low-dose aspirin;
- Use of **SBP** in diagnosis and management of PE/severe PE
- Use of **laboratory findings** for severe PE
- Use of **antihypertensive** in management of HTN, including acute severe systolic HTN
- **Anticonvulsant therapy** for severe PE/E
- **Timing of delivery** in women with severe PE and Eclampsia
- **Postpartum monitoring**
- **Specialized post-partum care and follow up**

Clinical Criteria for Diagnosis of HTN in Pregnancy

- **SBP ≥ 140 mm Hg** and/or DBP ≥ 90 mm Hg (two consecutive readings four hours or more apart)
- **Severe SBP ≥ 160** and /or DBP ≥ 110 mm Hg

Prevention

- **Calcium supplementation** (in areas with low dietary intake)
  - 1.5–2.0 g elemental calcium/day
  - All women, but particularly those **at high-risk of PE***
- **Low-dose (75 mg) acetylsalicylic acid (aspirin)**
  - Initiated **12 - 20 weeks of gestation** for women **at high risk of PE***

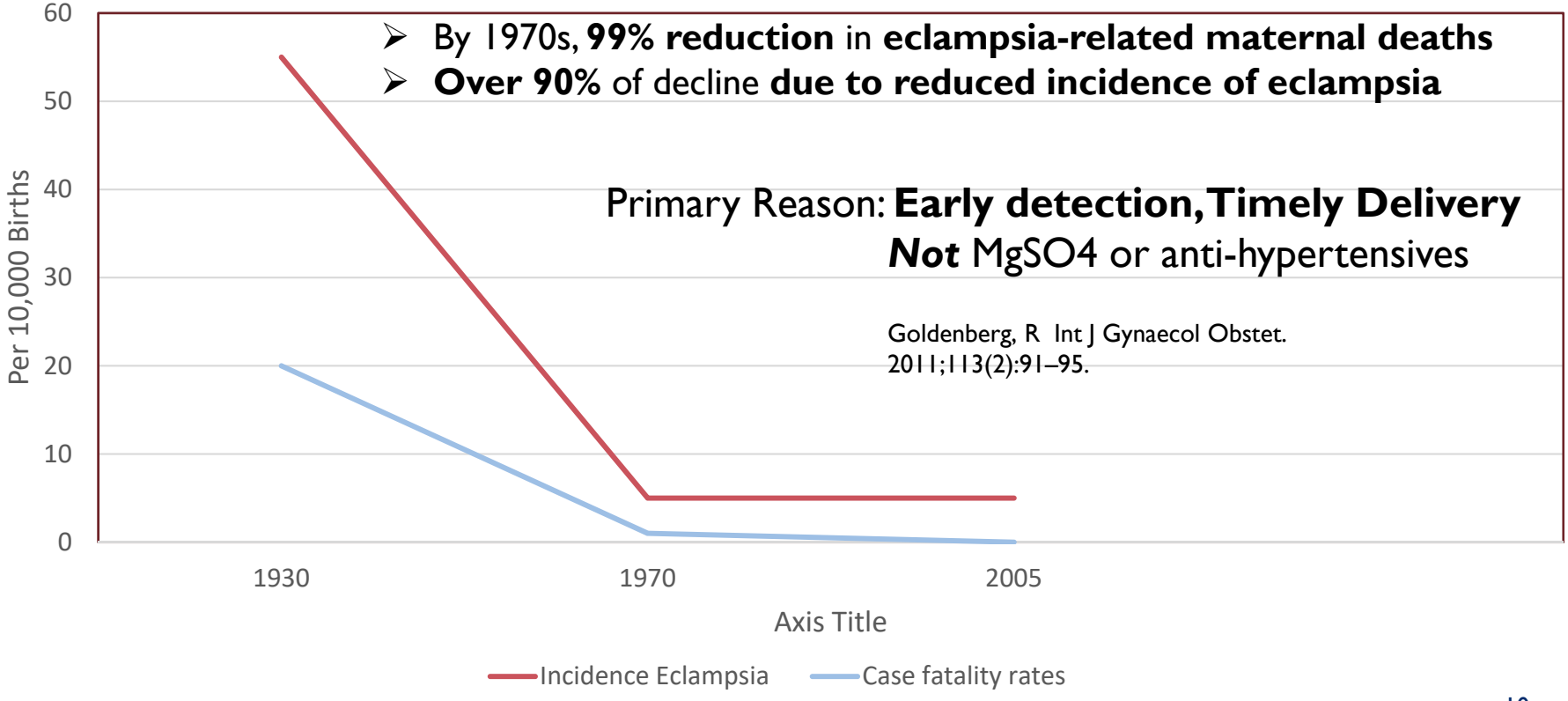
***Risk Factors for Developing PE/E:**

- Previous severe PE/E, diabetes, chronic hypertension, obesity, renal disease, autoimmune disease and multiple pregnancies.

Treatment of acute severe hypertension: *SBP ≥ 160 mmHg* and/or DBP ≥ 110 mmHg

Anti-hypertensive Options	Dosing
Hydralazine	**Intravenous treatment:** • Administer 5 mg IV, slowly; Repeat every five minutes until blood pressure goal is achieved. • Repeat hourly as needed or give 12.5 mg IM every 2 hours as needed. • The maximum dose is 20 mg per 24 hours.
Labetalol	**Oral treatment:** • Administer 200 mg; Repeat dose after one hour until blood pressure goal is achieved. • The maximum dose is 1200 mg in 24 hours. **Intravenous treatment:** • Administer 10 mg IV. If response is inadequate after 10 minutes, administer 20 mg IV. • The dose can be doubled to 40 mg and then 80 mg with 10-minute intervals between each increased dose until blood pressure is achieved. • The maximum total dose is 300 mg; then switch to oral treatment.
Nifedipine (immediate-release capsule)	**Oral treatment:** • Administer 5–10 mg orally. Repeat dose after 30 minutes until blood pressure goal is achieved. • The maximum total dose is 30 mg in the acute treatment setting.
Alpha Methyldopa	**Oral treatment:** • Administer 750 mg orally. • Repeat dose after three hours until blood pressure goal is achieved. • The maximum dose is 3 grams in 24 hours. Source: *Elevated blood pressure, headache, blurred vision, convulsions or loss of consciousness* chapter

Eclampsia: Trends in Incidence and Case Fatality Rates in High Income Countries



Severe Pre-Eclampsia: Diagnosis and Timing of Childbirth

Diagnosis of Severe Pre-Eclampsia

- **New onset hypertension and proteinuria after 20 weeks gestation:**
  - → SBP ≥160 and/or DBP ≥ 110 after 20 weeks of gestation
  - → Proteinuria 2+ on dipstick
- Pre-eclampsia **with any of the following present**, diagnose severe pre-eclampsia:
  - → **Neurologic**: Headache, vision changes, hyper-reflexia, clonus
  - → **Pulmonary**: difficulty breathing (rales on auscultation due to fluid in lungs)
  - → **Hepatic:** upper abdominal pain, nausea/vomiting, liver enzymes elevated > 2x baseline
  - → **Renal:** serum creatinine > 1.1 mg/dL or doubling of baseline, oliguria (< 400 cc urine 24 hrs),
  - → **Hematologic**: Platelets < 100,000 cells/mcL

Summary Guidance for Optimal Timing of Delivery for Severe Pre-Eclampsia

- **Gestational age < 24 weeks (pre-viable fetus)**
  - → $MgSO_4$, anti-hypertensive medications
  - → Induce labour
- **Gestational age 24-34 weeks**
  - → $MgSO_4$; anti-hypertensive medications; antenatal corticosteroids (ACS) if safety conditions met;
  - → Close maternal and fetal monitoring; expedite birth if maternal and fetus status not stable
- **Gestational age 34-36 6/7 weeks**
  - → Same management as for 24-34 weeks **except NO *ACS***
- **Gestational age 37 0/7 weeks**
  - → $MgSO_4$, anti-hypertensive medications and expedite delivery

Use of medicines in the management of PPH – new medications in 2nd edition

(Formerly: Use of Oxytocic Drugs)

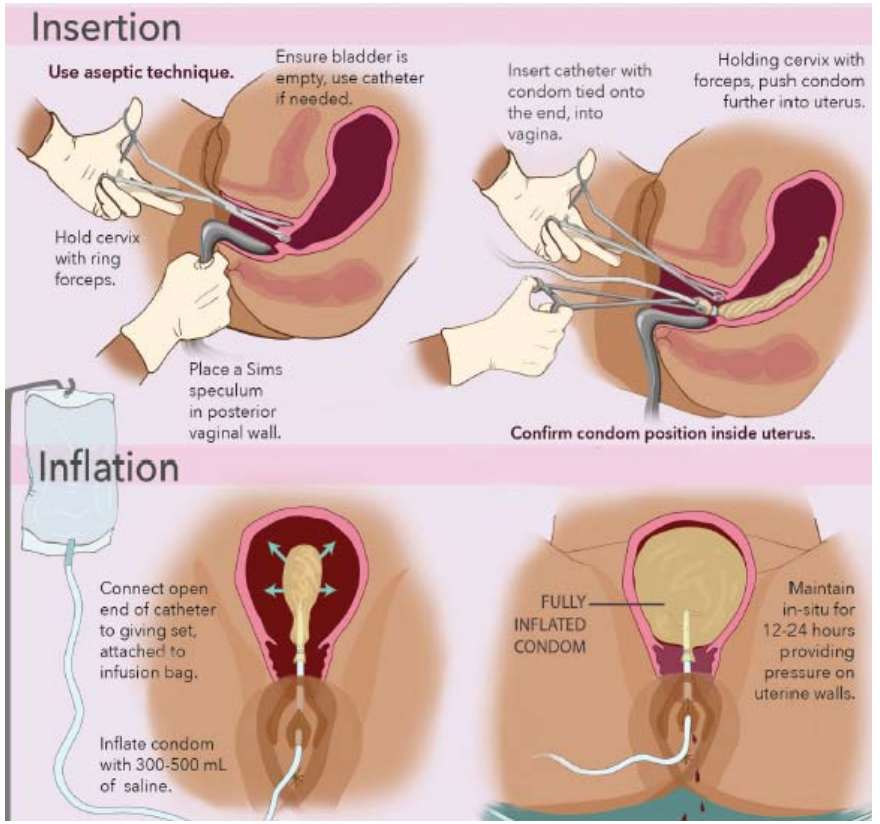
	Dose and Route	Continuing	Maximum Dose	Precaution and Contraindication
Misoprostol PGE1	Sublingual 800 mcg	Repeat 200-800mcg	Not more than 1600 mcg	
Tranexamic Acid	IV (slowly) 1g	Repeat after 30 mins if bleeding continues (adjusted for renal function)	Not more than 10mg/kg body weight, three to four times daily	History of coagulopathy or active intravascular clotting, convulsions

PPH Management

Sections added and/or revised:

- **Medicines** for PPH management
- **Nonpneumatic antishock garment**
- Surgical Interventions revised, including addition of **B-lynch suture**
- ➢ **Intrauterine Balloon Tamponade**

- IV Fluid Management
- Blood

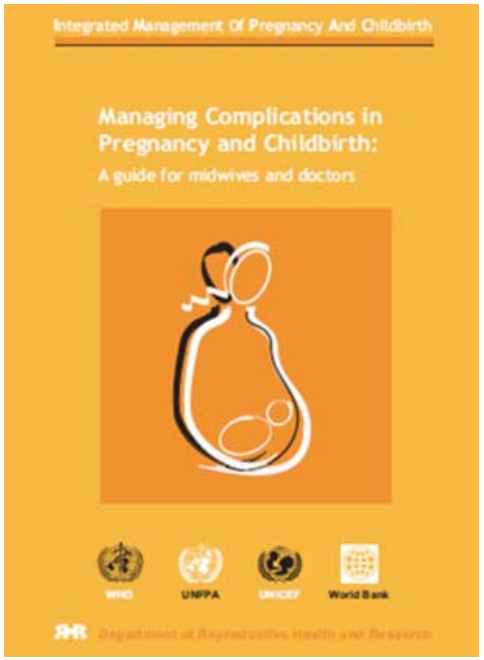


Summary of MCPC User Survey Findings (Prior to Revision): Significant Redesign is Needed

- While **organization** is useful (e.g., symptom-sign approach), it is **not particularly user friendly**
- **Guidelines not up to date**, which creates confusion
- Current format not responsive to large amount of emerging, new evidence constantly
  - **Real-time updating of individual chapters rather than the entire manual**
- Should Include **Clinical Algorithms**
- Should include more relevant **Illustrations** (e.g., UBT, B-Lynch)
- **Use of technology** to facilitate more rapid and effective publishing/dissemination of updated WHO recommendations

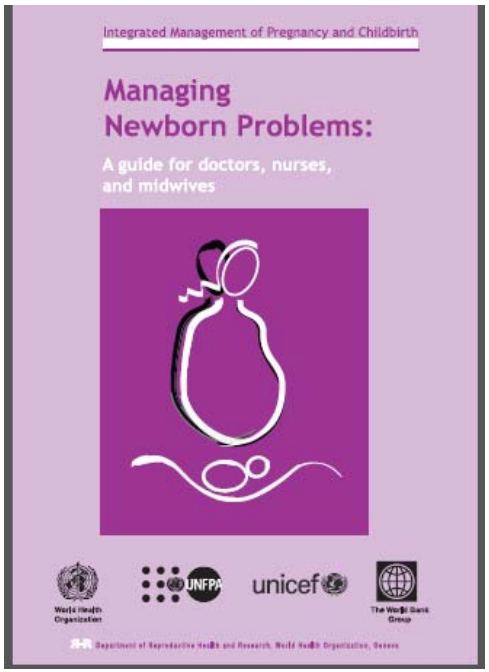
Integrated Management of Pregnancy & Childbirth (IMPAC) Manuals

Managing Complications in Pregnancy and Childbirth (MCPC)

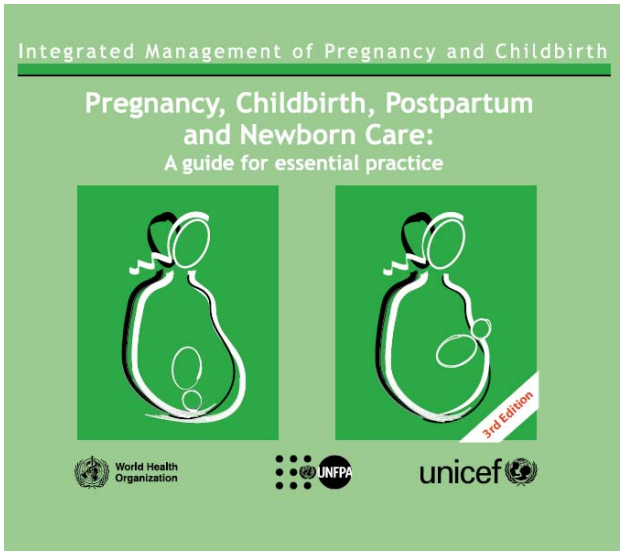


Symptom-sign, step-by-step approach

Managing Newborn Problems



Pregnancy, Childbirth, Postpartum and Newborn Care (PCPNC)



Flow chart syndromic approach, with links to treatment in other parts

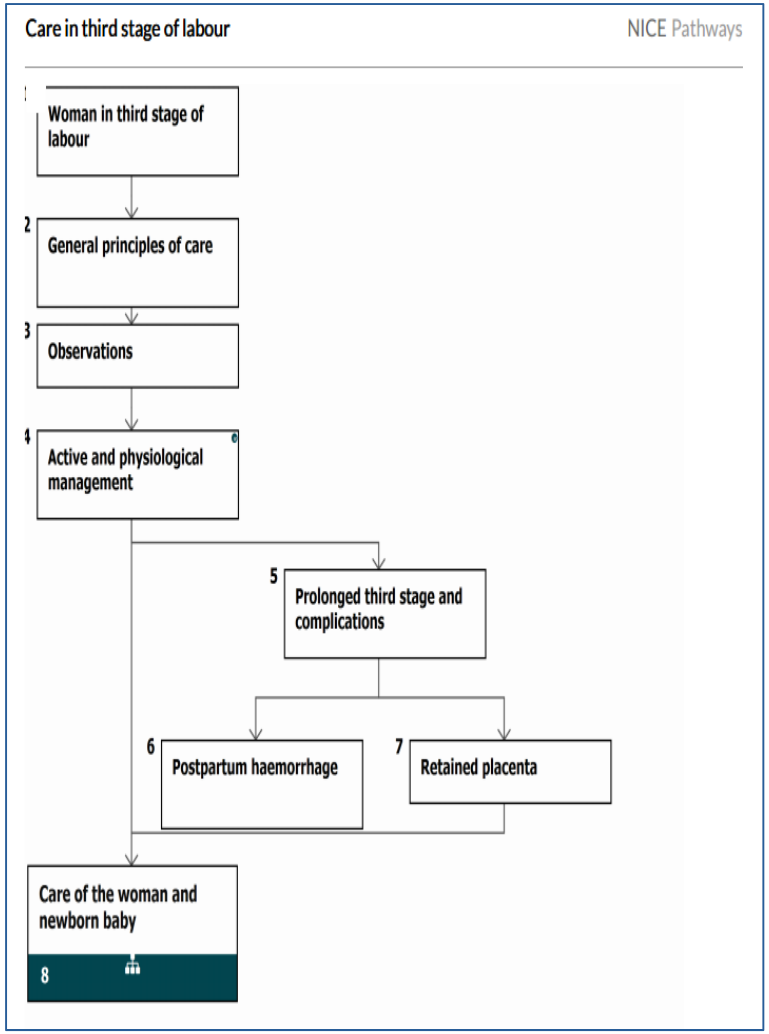
WHO Technical Meeting on 'Redesigning the WHO Guidelines Derivative Tools for Maternal and Perinatal Health' May 16-17, 2017

Considerations

- Urgent demand from countries for updated IMPAC materials
- WHO MNH recommendations (e.g. ANC) focus on specific questions and are not comprehensive - need for up to date comprehensive IMPAC guidance
- Compare use of clinical pathways/algorithms to other formats
- Unifying of MCPC/PCPNC content and format
- Digital vs paper
- Pragmatic approach - more iterative and rapid
- Regional differences, expectations, requirements
- Different levels of internet access
- Develop and pilot select content
- Pilot in a few settings to assess feasibility & acceptability
- End user testing: who, where, how

Next steps

- Adapt and unify MCPC/PCPNC platform
- Digital as primary process, with print PDF functionality
- By end of 2017
  - Agree on and develop new formats (pathway and 1 – 2 others) to test on same condition: one complication (e.g., PE/E) and one routine
  - Conduct targeted end user survey on formats
    - Clinical-based user testing of formats (different facility types, provider levels, location)
  - Iterative development of outputs
  - Develop larger, formal collaborative proposal and management structure for continuous revision process
  - Link with potential donors and partners



2018 and Beyond

- Based on 2017 learning, select a "primary" format
- Establish section editors, management structure, procedures etc.
- Start populating selected format with additional content (conditions)
- Develop full proposal
  - Becomes core component of QoC initiative to address knowledge gaps, provide best-practice evidence, etc

Summary

- MCPC has received much needed updates
- Process is arduous and present format does not optimally meet needs of end users
- Digital and clinical pathway/algorithm formats hold significant promise to meet needs of frontline health care worker

Thank you!

Tranexamic Acid and the WOMAN Trial Results

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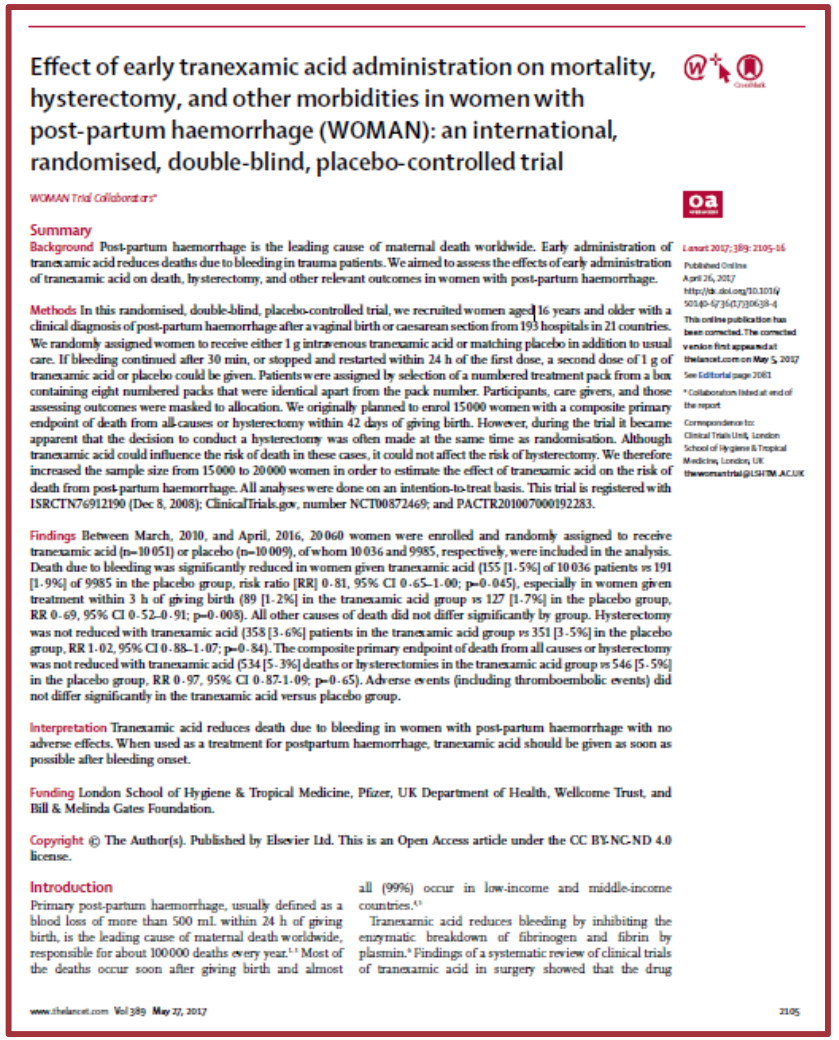
Outline

- WOMAN study results
- Implications of study results for management of PPH

- Randomized, double-blind, placebo-controlled trial
- Assesses the effects of early administration of tranexamic acid on death, hysterectomy, and other relevant outcomes in women with PPH
- March 2010 – April 2016, 20,060 women enrolled at 193 hospitals in 21 countries
- Women with PPH received TXA 1 gm IV* or matching placebo along with usual care (2nd dose if bleeding continued after 30 mins, or restarted within 24 hrs)



Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

WOMAN Trial Collaborators*

Summary

Background Post-partum haemorrhage is the leading cause of maternal death worldwide. Early administration of tranexamic acid reduces deaths due to bleeding in trauma patients. We aimed to assess the effects of early administration of tranexamic acid on death, hysterectomy, and other relevant outcomes in women with post-partum haemorrhage.

Methods In this randomised, double-blind, placebo-controlled trial, we recruited women aged 16 years and older with a clinical diagnosis of post-partum haemorrhage after a vaginal birth or caesarean section from 193 hospitals in 21 countries. We randomly assigned women to receive either 1 g intravenous tranexamic acid or matching placebo in addition to usual care. If bleeding continued after 30 min, or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given. Patients were assigned by selection of a numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Participants, care givers, and those assessing outcomes were masked to allocation. We originally planned to enrol 15 000 women with a composite primary endpoint of death from all causes or hysterectomy within 42 days of giving birth. However, during the trial it became apparent that the decision to conduct a hysterectomy was often made at the same time as randomisation. Although tranexamic acid could influence the risk of death in these cases, it could not affect the risk of hysterectomy. We therefore increased the sample size from 15 000 to 20 000 women in order to estimate the effect of tranexamic acid on the risk of death from post-partum haemorrhage. All analyses were done on an intention-to-treat basis. This trial is registered with ISRCTN76912190 (Dec 8, 2008); ClinicalTrials.gov, number NCT00872469; and PACTR201007000192283.

Findings Between March, 2010, and April, 2016, 20 060 women were enrolled and randomly assigned to receive tranexamic acid (n=10 051) or placebo (n=10 009), of whom 10 036 and 9985, respectively, were included in the analysis. Death due to bleeding was significantly reduced in women given tranexamic acid (155 [1·5%] of 10 036 patients *vs* 191 [1·9%] of 9985 in the placebo group, risk ratio [RR] 0·81, 95% CI 0·65–1·00; p=0·045), especially in women given treatment within 3 h of giving birth (89 [1·2%] in the tranexamic acid group *vs* 127 [1·7%] in the placebo group, RR 0·69, 95% CI 0·52–0·91; p=0·008). All other causes of death did not differ significantly by group. Hysterectomy was not reduced with tranexamic acid (358 [3·6%] patients in the tranexamic acid group *vs* 351 [3·5%] in the placebo group, RR 1·02, 95% CI 0·88–1·07; p=0·84). The composite primary endpoint of death from all causes or hysterectomy was not reduced with tranexamic acid (534 [5·3%] deaths or hysterectomies in the tranexamic acid group *vs* 546 [5·5%] in the placebo group, RR 0·97, 95% CI 0·87–1·09; p=0·65). Adverse events (including thromboembolic events) did not differ significantly in the tranexamic acid versus placebo group.

Interpretation Tranexamic acid reduces death due to bleeding in women with post-partum haemorrhage with no adverse effects. When used as a treatment for postpartum haemorrhage, tranexamic acid should be given as soon as possible after bleeding onset.

Funding London School of Hygiene & Tropical Medicine, Pfizer, UK Department of Health, Wellcome Trust, and Bill & Melinda Gates Foundation.

Introduction

Primary post-partum haemorrhage, usually defined as a blood loss of more than 500 mL within 24 h of giving birth, is the leading cause of maternal death worldwide, responsible for about 100 000 deaths every year.[1,2] Most of the deaths occur soon after giving birth and almost all (99%) occur in low-income and middle-income countries.[2,3]

Tranexamic acid reduces bleeding by inhibiting the enzymatic breakdown of fibrinogen and fibrin by plasmin.[4] Findings of a systematic review of clinical trials of tranexamic acid in surgery showed that the drug

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See Editorial page 2081

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*Dose: 100 mg/ml IV at 1 mL/min

Main Results

- **Deaths from bleeding** significantly **reduced by 19%** with use of TXA
- **Reduced by 31% if given within 3 hrs** of giving birth; no reduction if given after 3 hrs
- Risk of hysterectomy was not reduced
- Risk of laparotomy to control bleeding was significantly reduced (36%)
- Risk of thromboembolic events did not differ significantly

	Tranexamic acid group (n=10036)	Placebo group (n=9985)	RR (95% CI)	p value (two-sided)
Bleeding	155 (1·5%)	191 (1·9 %)	0·81 (0·65–1·00)	0·045
Pulmonary embolism	10 (0·1%)	11 (0·1)	0·90 (0·38–2·13)	0·82
Organ failure	25 (0·3%)	18 (0·2%)	1·38 (0·75–2·53)	0·29
Sepsis	15 (0·2%)	8 (0·1%)	1·87 (0·79–4·40)	0·15
Eclampsia	2 (0·02%)	8 (0·1%)	0·25 (0·05–1·17)	0·057
Other	20 (0·2%)	20 (0·2%)	0·99 (0·54–1·85)	0·99
Any cause of death	227 (2·3%)	256 (2·6%)	0·88 (0·74–1·05)	0·16

Data are n (%), unless otherwise indicated. RR=risk ratio.

Table 2: **Effect of tranexamic acid on maternal death**

Implications

- Administration of tranexamic acid to women with PPH significantly reduces death due to bleeding, with no evidence of adverse events/complications
- TXA should be given as soon as possible following onset of PPH (atony, trauma), and alongside use of uterotonics
  - Note: MCPC 2017 - If oxytocin and other uterotonics fail to stop the bleeding or if the bleeding may be partly due to trauma, administer tranexamic acid.
- Availability of IV tranexamic acid in LMICs
- Effectiveness/bioavailability of oral tranexamic acid

Thank you!

For more information, please visit
www.mcsprogram.org

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