

# Misoprostol for PPH : What else do we need to know?

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# Research on Misoprostol for PPH

➤ Misoprostol for **prevention** of PPH

Misoprostol for **primary treatment** of PPH

Misoprostol as **adjunct to treatment** of PPH

# A peek at relevant published studies...

Author & Location	Setting & Provider	Miso Dose & Route	Control Arm	Total (n)
<b>Derman,</b> India	Primary Health Center areas Midwives (ANMs)	600 µg, oral	Placebo	1,612
<b>Gulmezoglu,</b> Multi-center	Tertiary Care Facilities Hospital staff	600 µg, oral	Oxytocin 10 IU IM/IV	18,530
<b>Prata,</b> Egypt	University Hospitals Hospital staff	600 µg, oral	Standard PPH practice *	2,532
<b>Walraven,</b> The Gambia	Homebirth setting TBAs	600 µg, oral	Ergometrine 4x0.5mg tabs	1,229
<b>Zachariah,</b> India	Medical College Hospital Hospital staff	400 µg, oral	Oxytocin^ Ergometrine^	2,023

\* Oxy 5-10 IU (n=609); Ergo .2-.4mg (n=621), no uterotonic (n=94)

^ Oxy 10 U IM (n=617), Ergo 2mg IV (n=676)



# Misoprostol for PPH Prevention

## Community-based studies: What evidence is there now?

### Randomized-controlled trials

- Misoprostol is associated with a significant reduction in PPH (Derman, 2006)
- Blood loss outcomes are consistently lower in the misoprostol arm (Walraven, 2005)



# Misoprostol for PPH Prevention

## Hospital-based studies: What evidence is there now?

### Randomized-controlled trials

- Misoprostol is associated with a significantly higher rate of blood loss (WHO, 2001).
- Misoprostol (400µg) is as effective as conventional oxytocics (Zachariah, 2006).



# Misoprostol for PPH Prevention

**Hospital-based studies:  
What evidence is there now?**

## Operations research study

- Compared to standard PPH prevention practice in real ward conditions (Egypt), misoprostol resulted in a significantly lower rate of blood loss (Prata, 2006).



# Misoprostol for PPH Prevention

## Ongoing Research: Community-based studies

**Purpose** Determine the impact of misoprostol (600 µg oral) on reducing postpartum blood loss when administered by TBAs in home-birth settings

- Randomized placebo-controlled trial, Pakistan, n=1,600
- Intervention vs. non-intervention, Bangladesh, n=1,000+
- Intervention vs. non-intervention, Ethiopia, n=1,000+
- Other ongoing research in rural, home-birth settings (?)...



# Misoprostol for PPH Prevention

## Ongoing Research: Hospital-based studies

**Purpose** Determine the impact of misoprostol (600 µg oral) on reducing postpartum blood loss in hospital settings where oxytocics are not available or not routinely used

- Randomized placebo-controlled trial, Tibet, n=848
- Randomized controlled trial, Bangladesh, n=3,000

**Purpose** Determine the impact of misoprostol (400 µg oral) as adjunct prophylaxis

- Randomized placebo-controlled trial, multi-country, n=1,200



# Misoprostol for PPH Prevention

## What else do we need to know?

- Evidence shows that misoprostol reduces the incidence of PPH, but will this translate into saving women's lives?
- Where will women most benefit from misoprostol for PPH prevention?
- Miso has been proven effective in clinical trials, but how will this effect translate when miso for PPH programs are operationalized?
- Side effects with a 600µg misoprostol are minimal, so should efficacy/safety of a lower dose be explored?
- Many care providers do not currently practice AMTSL, so will they be trained to administer miso as part of AMTSL or will they be trained to use miso alone?



# Research on Misoprostol for PPH

➤ Misoprostol for **treatment** of PPH

Misoprostol as **adjunct to treatment** of PPH



# Misoprostol for PPH Treatment

## A peek at the published literature...

- 8 uncontrolled studies and 3 randomized controlled trials (RCTs) on misoprostol for PPH treatment
- Range of doses and routes studied
- Variation in inclusion criteria and outcome measures
- Criteria and timing of miso administration varied – given as first line treatment, second line treatment, or last resort

# Uncontrolled Studies

First author	Year	Subjects (n)	Misoprostol regimen	Max dose
O'Brien	1998	14	1000 µg rectal	1000
Ozan	2000	2	400 µg oral, repeated	1200
Abdel-Aleem	2001	18	600 µg or 1000 µg rectal	1000
Shojai	2001	5 <sup>a</sup>	200 µg rectal	1000
Adekanmi	2001	1	800 µg intra-uterine	800
Oboro	2003	1	800 µg intra-uterine	800
Shojai	2004	41	1000 rectal	1000
Prata	2005	849	1000 rectal	1000

# Randomized Controlled Trials

First author	Year	(N)	Regimens	Total dose
Lokugamage	2001	64	800 µg rectal vs. syntometrine + IV syntocinon	800 µg
Walraven	2004	160	200 µg oral, 400 µg sublingual vs. standard oxytocics	600 µg
Hofmeyr	2004	238	200 µg oral, 400 µg sublingual, 400 µg rectal vs. standard oxytocics	1000 µg



# Misoprostol for PPH Treatment

## What evidence is there now?

- Fewer than 800 women have had their PPH treated with misoprostol in these published studies
- Misoprostol shows a clinically important effect
  - prompt uterine contraction after administration
  - trend in blood loss reduction
- Side effects mild/transient; shivering/pyrexia common \*
- Insufficient data to support specific regimen for txt
  - for misoprostol in addition to oxytocin
  - for misoprostol alone as first line treatment

\* 3 cases of severe pyrexia reported (>40 C) using dose of 1000µg



# Misoprostol for PPH Treatment

## Current Research Questions:

- Is misoprostol effective in controlling primary PPH due to uterine atony?
  - as first line treatment
  - as adjunct treatment
- What is the optimal dose and route of misoprostol for PPH treatment?
- Are the side effects minimal and acceptable for women?



# Misoprostol for PPH Treatment

## Ongoing Research: Miso as primary treatment

**Purpose** Test if misoprostol is as effective as oxytocin for the treatment of primary PPH due to uterine atony

**Study Arms** 1,900 women diagnosed with PPH are randomized to receive:

- 800  $\mu\text{g}$  sublingual misoprostol or
- 40 IU oxytocin

**Study Setting** Hospitals in Burkina Faso, Ecuador, Egypt, Turkey, Vietnam

**Collaborators** Gynuity, FCI, and Country Partners



# Misoprostol for PPH Treatment

## Ongoing Research: Miso as primary treatment

**Purpose** Determine whether TBAs can effectively diagnose and treat PPH with 1000 $\mu$ g rectal misoprostol

**Study Design** Intervention vs. non-intervention

**Study Setting** Homebirths (n=1,000) in Nigeria

**Collaborators** UC-Berkeley, Venture Strategies, and partners in Nigeria



# Misoprostol for PPH Treatment

## Ongoing Research: Miso as adjunct treatment

**Purpose** Test if misoprostol in addition to standard PPH care is more effective than injectable oxytocics alone

**Study Arms** 1,400 women diagnosed with PPH are randomized to receive additional treatment of:

- 600 µg sublingual misoprostol or placebo

**Study Setting** Hospitals in Argentina, Egypt, South Africa, Thailand, Vietnam, and Pakistan

**Collaborators** WHO, Gynuity and, AKU & AKHS,P



# Misoprostol for PPH Treatment

## Ongoing Considerations:

- What are the training implications for use of misoprostol to treat primary PPH?
- Do the benefits of misoprostol outweigh the disadvantages of its side effects? In some settings/all?
- If current regimens studied are proven highly effective, should efficacy/safety of a lower dose be explored?

# Moving Forward...

- ✓ **Monitoring & Evaluation** of all new misoprostol PPH programs is essential to understand its real world impact.
- ✓ **Impact on MMR and safety** should be key component of M&Es.
- ✓ **Training modules** and their components should be developed and tested.
- ✓ **Role of Uniject** should be further explored.
- ✓ **Registration** – Clinical evidence should be used to register misoprostol for this indication with regulatory bodies.
- ✓ ...