Addressing the Leading Cause of Maternal Mortality Worldwide

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Preventable Deaths Every Day

- 830 women die during pregnancy and childbirth everyday
- 287,000 maternal deaths every year (total 303,000)
- 56,000 maternal deaths every year in India

WHO, State of World's Mothers Report 2015

Why Do Women Die?

- Major complications account for 80% of all maternal deaths
- Severe bleeding (primary PPH) – 35%
- ↑ - BP (eclampsia, pre-eclampsia) – > 15 %
- Infections (usually manifest post delivery)
- Remainder primarily caused by malaria, AIDS and TB during pregnancy

WHO, 2012

The Challenge

- **Every 4 minutes a woman dies from postpartum hemorrhage (PPH – 35% of all maternal deaths)**

- **Global action to address PPH comprehensively is a public health imperative.**

USAID/CHIP 2012/ACOG, 2015

What have we learned about reducing the incidence of PPH from hundreds of published clinical trials?

Active Management of the Third Stage of Labor (AMTSL)

- Designed to speed the delivery of the placenta by increasing uterine contractions and thus averting uterine atony
- Components
  - Administration of uterotonic agent (post cord-clamping)
  - Early cord clamping
  - Placenta delivered by controlled cord traction with counter-traction on the fundus

FIGO Joint Statement June, 2004

Two Methods of Third Stage Management

- **Physiologic (expectant) management**
  - **Oxytocics are not used**
  - **Placenta is delivered by gravity and maternal effort**

Physiologic Management: Advantages and Disadvantages

- Advantages
  - Does not interfere with normal labor process
  - Does not require special drugs/supplies
- Disadvantages
  - Increases the amount of blood loss after childbirth and the risk of postpartum hemorrhage (PPH)

Active vs. Physiologic Management: Postpartum Hemorrhage

	Active Management	Physiologic Management	OR and 95% CI
Bristol Trial	**50/846 (5.9%)**	**152/849 (17.9%)**	**3.13 (2.3-4.2)**
Hinchingbrooke Trial	**51/748 (6.8%)**	**126/764 (16.5%)**	**2.42 (1.78-3.3)**

Prendiville et al 1988; Rogers et al 1998.

Active Management of 3rd Stage of Labor

- 5 Randomized trials
- Cochrane review
- N = > 6,000
- NNT: Prevent PPH 500 ml - 12

  Severe PPH 1000 ml - 55

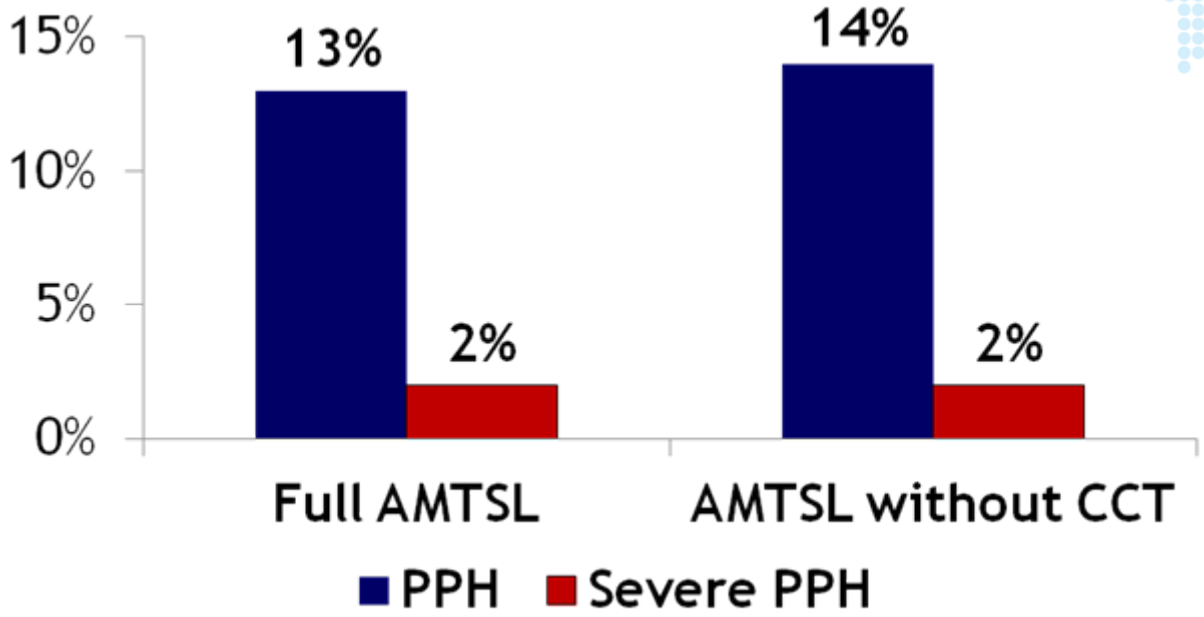
Active Management of the Third Stage of Labor Without Controlled Cord Traction

A Randomized Non-inferiority Controlled Trial

- **Concern over controlled cord traction in rural areas among non-physicians**
- **If not significant change in bleeding, can recommend against the practice and expand AMTSL to lower level providers**
- **Results indicate minimal benefit from CCT**
  - **PPH rates 9.8% vs 10.3%, NS**
  - **Less need for manual removal of placenta in CCT group, 4.29% vs 6.1% (RR 9.69)**
  - **3rd stage of labor > 15 minutes 4.59% vs 14.3% (P 0.31)**

Deneux – Thoraux, K., et al., BMJ, 2013 j 346: f1541

AMTSL with and without CCT on PPH prevention



World Health Organization

Gülmezoglu et al, Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. Lancet. 2012

Uterotonic Drugs

- Oxytocin-posterior pituitary extract
- Ergometrine-preparation of ergot
- Syntometrine-combination of oxytocin and ergometrine
- Misoprostol-prostaglandin E1 analogue
- Carbetocin (large multi-site clinical trial)

This is where our story begins…

NICHD Global Network Mission

Funded in 2001 by National Institute of Child Health and Human Development and the Bill & Melinda Gates Foundation to expand scientific knowledge, develop sustainable research infrastructures, and improve health outcomes for pregnant women and young children in developing countries.

Study Sponsors

National Institute of Child Health & Human Development

BILL & MELINDA GATES *foundation*

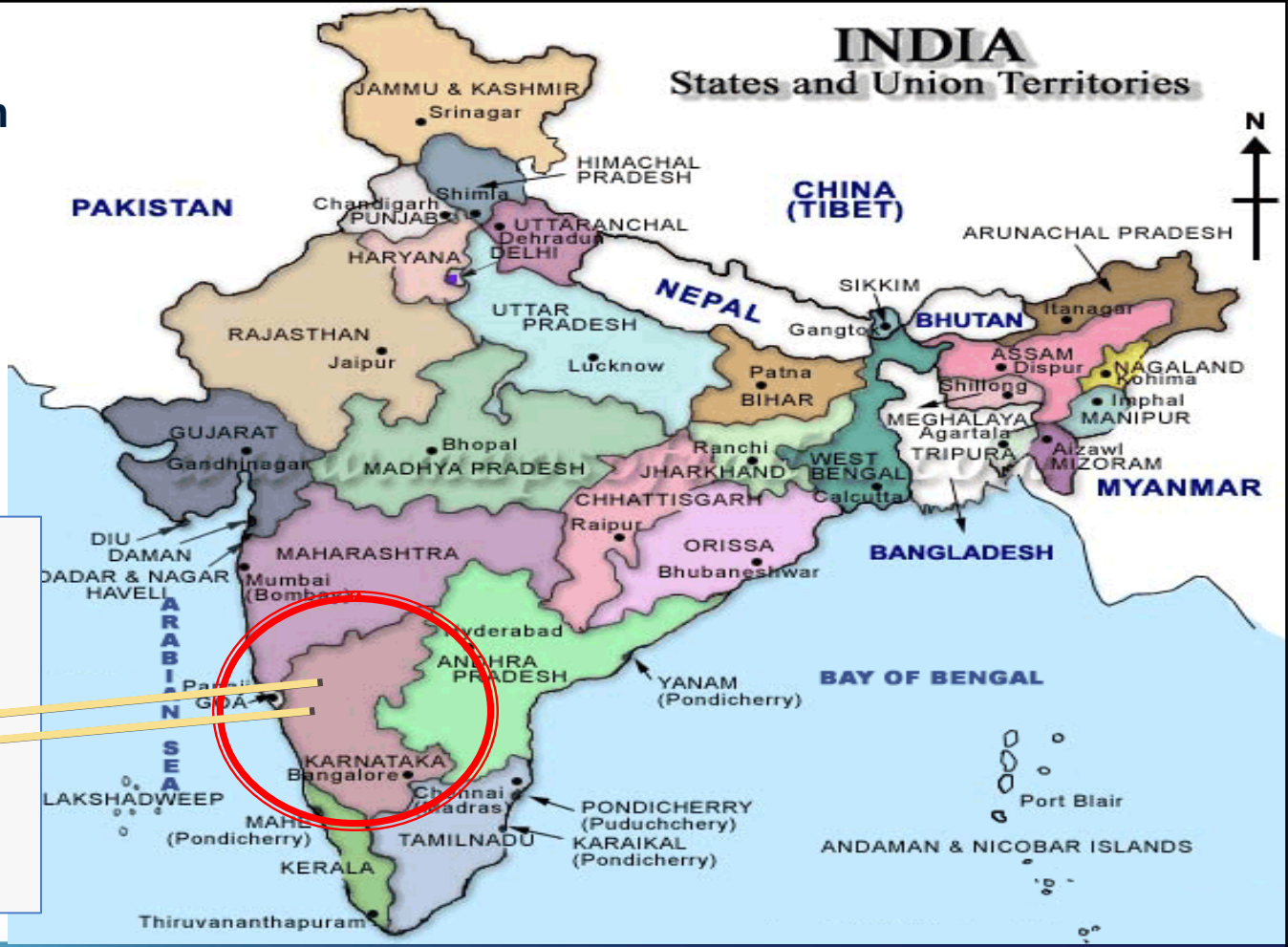
Bringing innovations in health and learning to the global community

2001

NICHD Global Network for Women's and Children's Health Research

RESEARCH SITE:

- **Originally in the Belgaum District**
- **Now in Belgaum and Bagalkot Districts—both are in the south India state of Karnataka**



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Greetings!

KLE University's Jawaharlal Nehru Medical College, Belgaum

Narendra Modi, Prime Minister of India

KLE Centenary Celebrations – November 13, 2017

Global Network Site 8: Research Agenda

- Postpartum Hemorrhage
- Hypertensive Disorders of Pregnancy
- Maternal Nutrition
- Birth Asphyxia
- Preterm Birth
- Infant neurodevelopment
- Emergency Obstetric and Neonatal Care

Our First Trial

Primary Hypothesis

Misoprostol administered during the third stage of labor will significantly reduce the incidence of acute postpartum hemorrhage by 50%.

N=1600

Intervention

- Misoprostol or Placebo, #3, 200 mcg tablets orally
- Administered within 5 minutes of clamping and cutting of the cord and cessation of cord pulsation

Key Elements of Study Protocol

- Skilled birth attendant
- Prophylactic uterotonic as intervention
- Delivery of placenta
  - Expectant Management
- Quantitative measurement of blood loss

Measuring postpartum blood loss

- **BRASSS-V® blood collection drape with calibrated receptacle**
- **The drape is used in <u>both</u> arms**

Patel A, *et al*. Drape estimation vs. visual assessment for estimating postpartum hemorrhage. Int J Gynaecol Obstet. 2006 Jun

BRASSS-V Blood Collection Drape with Calibrated Receptacle


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OB Clinic and Labor & Delivery

Number Needed to Treat (NNT)

One case of postpartum hemorrhage was prevented for every 18 women who received misoprostol

PPH ↓ 47%

Severe PPH ↓ 80%

India: Misoprostol to Prevent PPH

THE LANCET

Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial

Richard J Derman, Bhalchandra S Kodkany, Shivaprasad S Goudar, Stacie E Geller, Vijaya A Naik, M B Bellad, Shobhana S Patted, Ashlesha Patel, Stanley A Edlavitch, Tyler Hartwell, Hrishikesh Chakraborty, Nancy Moss

Lancet 2006; 368: 1248-53

Confirmatory Study on Prophylactic Use of Oral Misoprostol (600 mcg) n=1600

- Conducted in rural Pakistan
- Measured blood loss
- Outcome measures similar to India study

Gynuity Health Projects

Oral Misoprostol Trial: Global Public Health Impact

Inclusion in:

- **Guidelines of MOH, Government of India**
- **FIGO-ICM Guidelines**
- **WHO List of Essential Medicines**
- **UN Life-Saving Commodities for Women and Children**

Registration in 26 countries

Misoprostol for Self-Administration:

- Uganda (Mama Miso Study)
- Indonesia (JHPEIGO)
- Afghanistan (JHPEIGO)


MisoSafe
misoprostol
SFH
Society for Family Health
TOYOTA LAND CRUISER

Management of PPH in Low Resource Settings

PPH Non-Predictable

- Two-thirds of women who hemorrhage have no identifiable risk factors

- Women who survive often must receive blood transfusion - ↑ risk of hepatitis or HIV

WHO Mother-baby Package 1998

Average Interval from Onset to Death

- **Ruptured uterus** — **24 hours**
- **Antepartum hemorrhage** — **12 hours**
- **Postpartum hemorrhage** — **2 hours**

Maine D. Safe Motherhood Programs: Options and Issues,
Center for Population & Family Health, Columbia University,1993

Treatment of PPH with Sublingual Misoprostol vs Oxytocin (no prior uterotonic)

Ecuador, Egypt, Vietnam n=9,348 10% PPH rate

- Small differences in outcomes favoring IV oxytocin 40 IU *(bleeding controlled in 20 min 96% vs 90%)
- Additional blood loss ≥ 300ml 17% vs 30%
- 2 Minutes (50ml) difference in cessation of bleeding

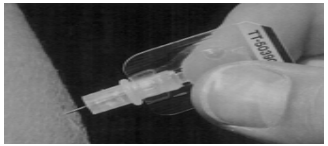
*10 IU oxytocin – no significant difference

(Potential use of new pharmaceutical agents, i.e. tranexamic acid)

Winikof, B et al. The Lancet, Jan 2010

Management of PPH Low Resource Settings

- Aggressive Treatment of PPH
  - Misoprostol 800-1000 mcg rectally
  - UNIJECT® - Oxytocin
    - Prefilled, nonrefillable, sterile
    - Single dose
    - Auto-disable syringe



Management of PPH Low Resource Settings

Uterine tamponade

- 90% of PPH in under-resourced countries due to uterine atony
- Hydrostatic Balloon Catheters

Sayeba Akhter, Use of a Condom to Control Massive Postpartum Hemorrhage, www.medscape.com/viewarticle/459894

Cook “Bakri” Intrauterine Balloon

- **There are now several balloons, but the most available in the US is the Cook “Bakri” Balloon**
  - **Specifically designed for this purpose**
  - **Double lumen** (for drainage from above)
  - **Silicone (non-latex)**
  - **Uterine contour shape**
  - **Good filling capacity (saline)**
  - **Inexpensive**
  - **Easy to use**

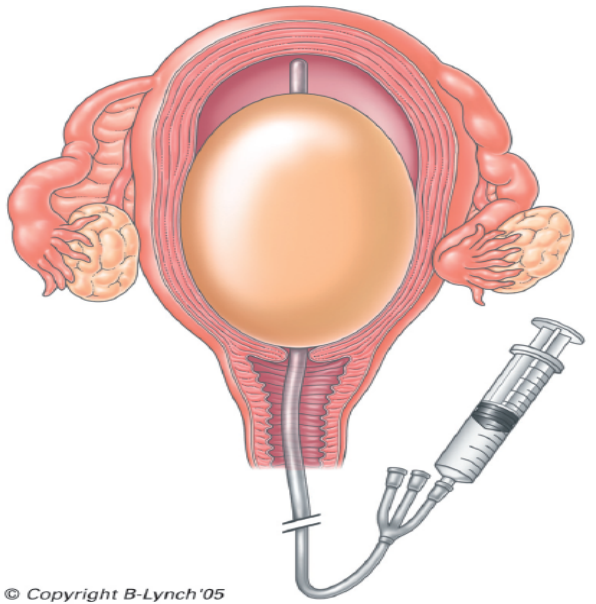


Figure 3 Bakri balloon

Tying the condom to the catheter

Introducing the catheter in the uterus

Inflated condom in a kidney tray

Anti-shock Garment

- Relatively low-cost neoprene suit (resembles bottom half of diver's wet suit)
- Pilot testing completed in Nigeria, Mexico and Egypt
- $11 million given by MacArthur Foundation (through Pathfinder) to expand use in Nigeria and India
- Multisite global randomized trial recently completed

  NASG vs standard of care

  RR = 0.52 for mortality

  (CI 0.36 - 0.77)

Miller SE, Journ Mid and WH, 2004

Non-inflatable Anti-shock Garment

New Drugs to Prevent or Treat PPH

Tranexamic Acid

- Prevents breakdown of fibrin and helps to maintain clotting
- Cochrane review-
  - 12 trials (N=3285) ↓ blood loss after delivery
- WOMAN trial
  - N=20,000 – 20% reduction in blood loss

Carbetocin - heat stable relative of oxytocin

- Positive side effect profile
- Significant reduction in post-c/s blood loss
- Major WHO trial (includes our site) ongoing

Maternal Mortality - India
The Good News Story

59% ↓ in MMR 1990-2008

- 1990 – 570/100,000
- 1995 – 470
- 2000 – 390
- 2005 – 280
- 2008 – 230
- 2015 - 178

World Bank, 2015

Maternal Mortality - India
The “Not So Good” Story

- India leads all countries in maternal mortality (19 %)
- Wide geographic differences in mortality within India
- Rate of anemia approximates 50%

Image: Wikipedia

Motherhood in India

- Mumtaz, the queen of Shah Jehan, may have died from post-partum hemorrhage while giving birth to her 14th child. The Taj Mahal was built in her memory.
- Motherhood in India is about as safe now as it was in Europe 100 years ago.
- In India, one maternal death occurs every 5 minutes.

Maternal Mortality Due to PPH in the Developing World

- Poor access to skilled providers/suppliers
- Poor transport systems
- Poor emergency services
- Poor clinic/hospital infrastructure despite ↑ in number of facility births

Facility Births
Bending the Benefit Curve

- Positive outcomes where OB/Peds and Anesthesia are available
- Where blood products/IV antibiotics available
- Where outcome data is accurate and acted upon
- Where team training has been instituted (use of checklists)

Google image

Special Thanks

World Health Organization

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

Indian Council of Medical Research — New Delhi

American Academy of Pediatrics — Dedicated to the health of all children™

Laerdal — helping save lives

Norad

RTI International

Gynuity Health Projects

United States Agency International Development — USAID — From the American People

UKaid — from the British people

Thrasher Research Fund

Department of Biotechnology
Ministry of Science & Technology,
Government of India

Thank you

Image source: Pixabay