

Preterm Birth Prevention Progesterone and Nitroglycerine



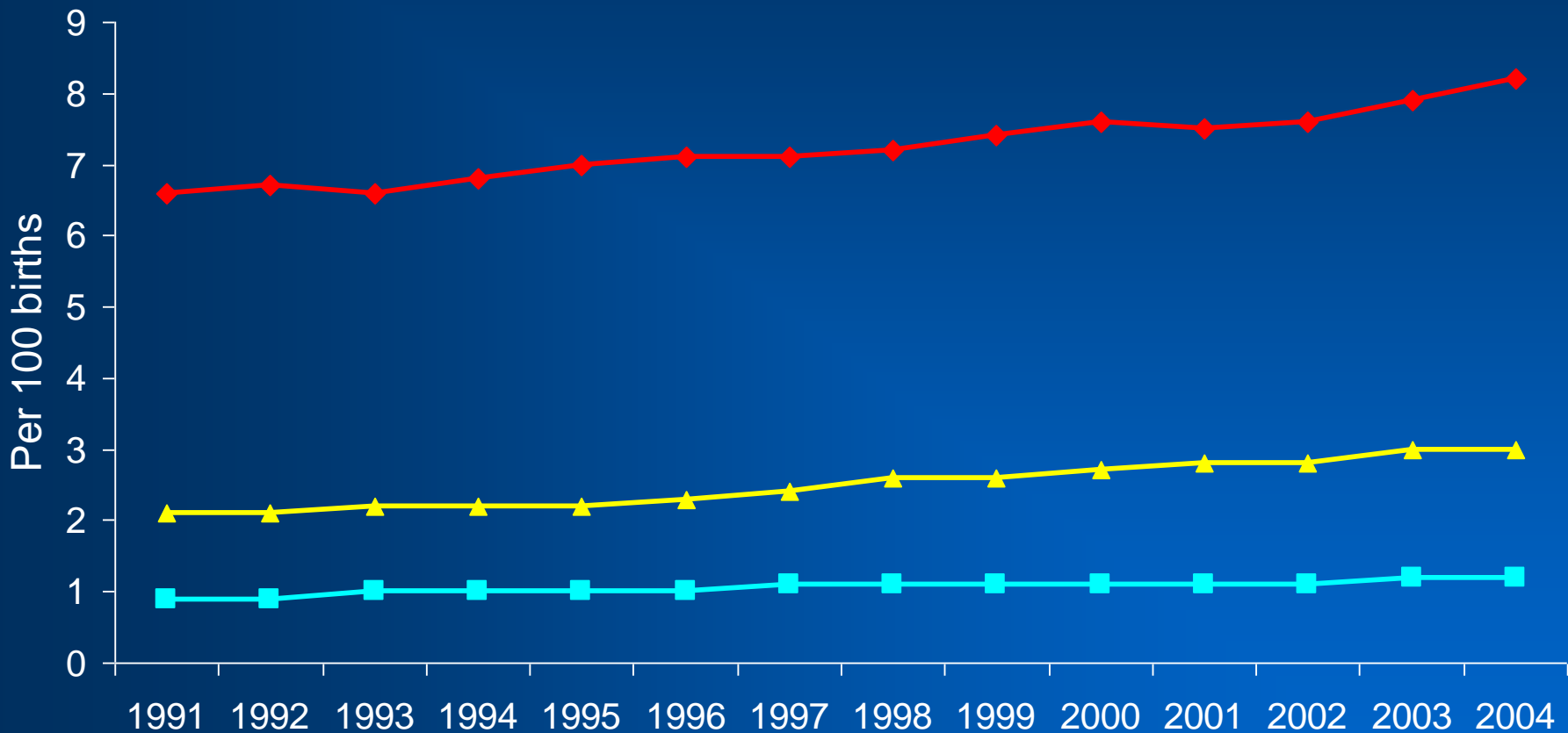
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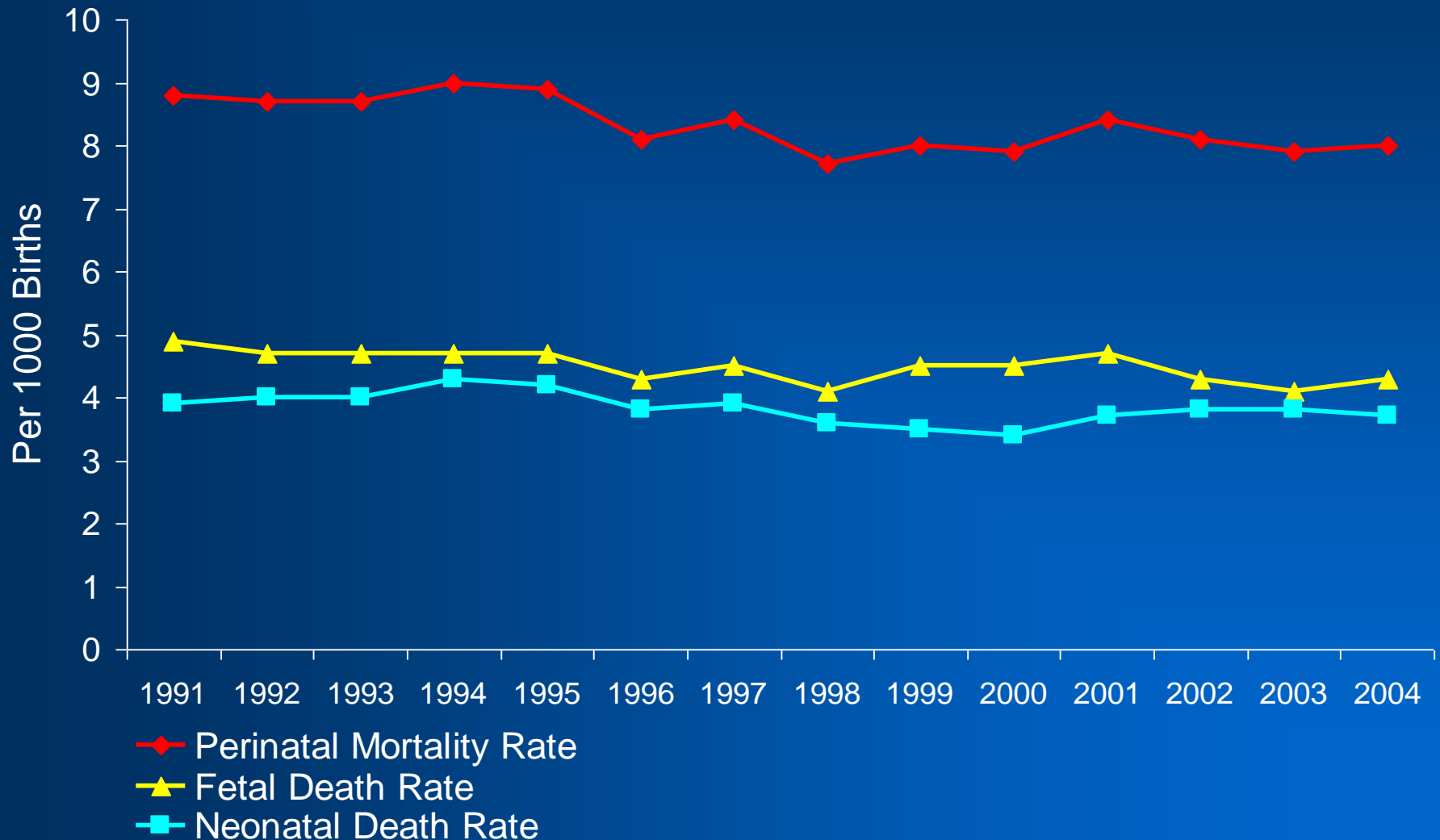
Preterm and Multiple Birth in Canada



- ◆ Preterm Births (< 37 weeks) per 100 live births
- Early Preterm Births (< 32 weeks) per 100 live births
- ▲ Multiple Births per 100 total births

Canadian Perinatal Health Report 2007 (in press)

Perinatal Mortality in Canada



Canadian Perinatal Health Report 2007 (in press)

Preterm Birth Prevention

Primary: population-based strategies

Secondary: interventions in high-risk pregnancies *Progesterone*

Tertiary: treatment of preterm labour

Progesterone

- Available for commercial use since 1934
- Infertility, menstrual disorders, uterine cancer, recurrent miscarriage
- Synthetic progestins
- Natural progestins
 - micronized for improved bioavailability
 - oral
 - vaginal
 - intra-muscular (17 α -OH P)

Proposed Mechanisms of Action for Preterm Birth Prevention

- Blocks oxytocin effect of prostaglandin $F_{2\alpha}$
- Blocks prostaglandin induced labour
- Prevents formation of gap junctions
- Relaxes myometrial smooth muscle
- Suppresses calcium-calmodulin-light chain kinase system → ↓ calcium influx

Randomized Controlled Trials

Da Fonseca *Am J Obstet Gynecol* 2003; 188: 419-24

- 142 high-risk singletons, Sao Paulo, Brazil
 - Prior PTB, cervical suture, uterine abnormality
- Vaginal suppository (100mg) daily
 - 24 to 34 weeks
- Decreased preterm birth
 - < 37 weeks (13.8% vs 28.5%)
 - < 34 weeks (2.8% vs 18.6%)
- No perinatal outcomes reported

Randomized Controlled Trials

Meis *NEJM 2003; 348: 2379-85*

- 463 singleton women, NIH MFMU Network
 - Prior spontaneous preterm birth
- 17OHP 250 mg IM weekly
 - 16-20 to 36 weeks
- Decreased preterm birth
 - < 37 weeks (36.3% vs 54.9%)
 - < 32 weeks (11.4% vs 19.6%)
- No difference in perinatal outcomes

ACOG Committee Opinion

- Need to evaluate progesterone prophylaxis in other high-risk groups:
 - multiple gestation
 - short cervix
 - positive *fFN* test
- Restrict progesterone use to women with prior spontaneous preterm birth

Estimated Effect of 17P on Preterm Birth in USA

- Singleton births to multiparous women
 - 2,300,000
- Previous spontaneous preterm birth
 - 131,000
- Recurrent preterm birth – 30,000
- Annual reduction in SPTB – 10,000
(12.1-11.8%)
 - In Canada ~ 1,000 (8.4-8.2%)

Survey of Canadian Obstetricians

- 1508 surveyed, 653 returned (43%)
- 7% offered progesterone to prevent SPTB
- Lack of evidence principal reason for not offering progesterone (71%)
- 84% willing to participate in large multicentre RCT

Progesterone Use in USA

Survey of 1264 MFMs - 572 returned(45%):

Used progesterone to prevent SPTB

2003 – 38%

2005 – 67%

Indications other than prior SPTB – 38%

Users concerned about insurance coverage

Nonusers concerned about safety, efficacy,
long term neonatal effects, more data

Randomized Controlled Trials

Rouse DJ *NEJM* 2007;357:454-61

- 661 women with healthy twin pregnancies
- 17 OHPC 250 mg weekly, 16-20 to 35 wks
- PTB<35 weeks
 - 17P 135/325 (42%)
 - Placebo 123/330 (37%)
- Perinatal morbidity/mortality
 - 17P 128/632 (20%)
 - Placebo 117/648 (18%)

Randomized Controlled Trials

Fonseca EB *NEJM* 2007;357:462-9

- 250 women with cervical length <15mm
- Vaginal progesterone 200mg daily, 24-34 wks
- Decreased preterm birth < 34 weeks
 - 19% vs 34%
- Neonatal morbidity
 - 8.1% vs 13.8% (NS)

Randomized Controlled Trials

O'Brien JM *Ultrasound Obstet Gynecol* 2007;30:687-96

The PROTERM Trial

- 659 singletons with previous preterm birth
- Vaginal 8% progesterone gel 90mg (Prochieve) daily from 18-22 wks to 37wks, delivery or PROM
- Primary Outcome: Preterm Birth \leq 32 weeks
- No difference in PTB or gestational age at delivery

SOGC Technical Update

- Women at risk for PTL should be encouraged to participate in studies on progesterone prophylaxis
- Women should be informed of current evidence:
 - Lack of effectiveness in preventing serious neonatal outcomes
 - Possible benefit in women with short cervix
- Prior PTB and short cervix <15mm could be used as indication for progesterone prophylaxis
- Recommended dosage
 - Prior PTB: 17P 250 mg IM weekly
 - Short cervix: Vaginal progesterone 200mg daily

Systemic Review

- 11 RCTs (2,425 women; 3,187 infants)
- Primary outcomes: perinatal death, PTB<34 wks, developmental delay
- Prior Spontaneous PTB
 - PTB<34wks: (1 study, 142 women) RR 0.15(0.04-0.64) NNT=7
 - LBW<2500g: (2 studies, 501 infants) RR 0.64(0.49-0.83) NNT=7
- Short Cervix
 - PTB<34wks: (1 study, 250 women) RR 0.58 (0.38-0.82) NNT=7
 - Neonatal sepsis: (1 study, 274 women) RR 0.28 (0.08-0.97) NNT=18

Systemic Review

- Multiple Pregnancy
 - PTB<37wks: No difference
 - Antenatal tocolysis: (1 study, 654 women) RR 0.75(0.57-0.97) NNT=14
- Threatened PTL
 - PTB<37wks: (1 study, 60 women) RR 0.29(0.12-0.69) NNT=5
 - LBW<2500g: (1 study, 70 infants) RR 0.52(0.28-0.98) NNT=5
 - RDS: (1 study, 70 infants) RR 0.30(0.11-0.83) NNT=3

Advantages of Vaginal Progesterone

- Increased bioavailability
- Rapid and efficient absorption
- Effective delivery to the uterus
- Lower daily dose requirement
- Continuous release formulation option
- Preference and acceptability
- Cost, safety and availability
 - Prometrium (Schering, Besins)
 - Prochieve (Columbia Laboratories)
 - Progesterone pessaries (Orion)

Preterm Birth Prevention

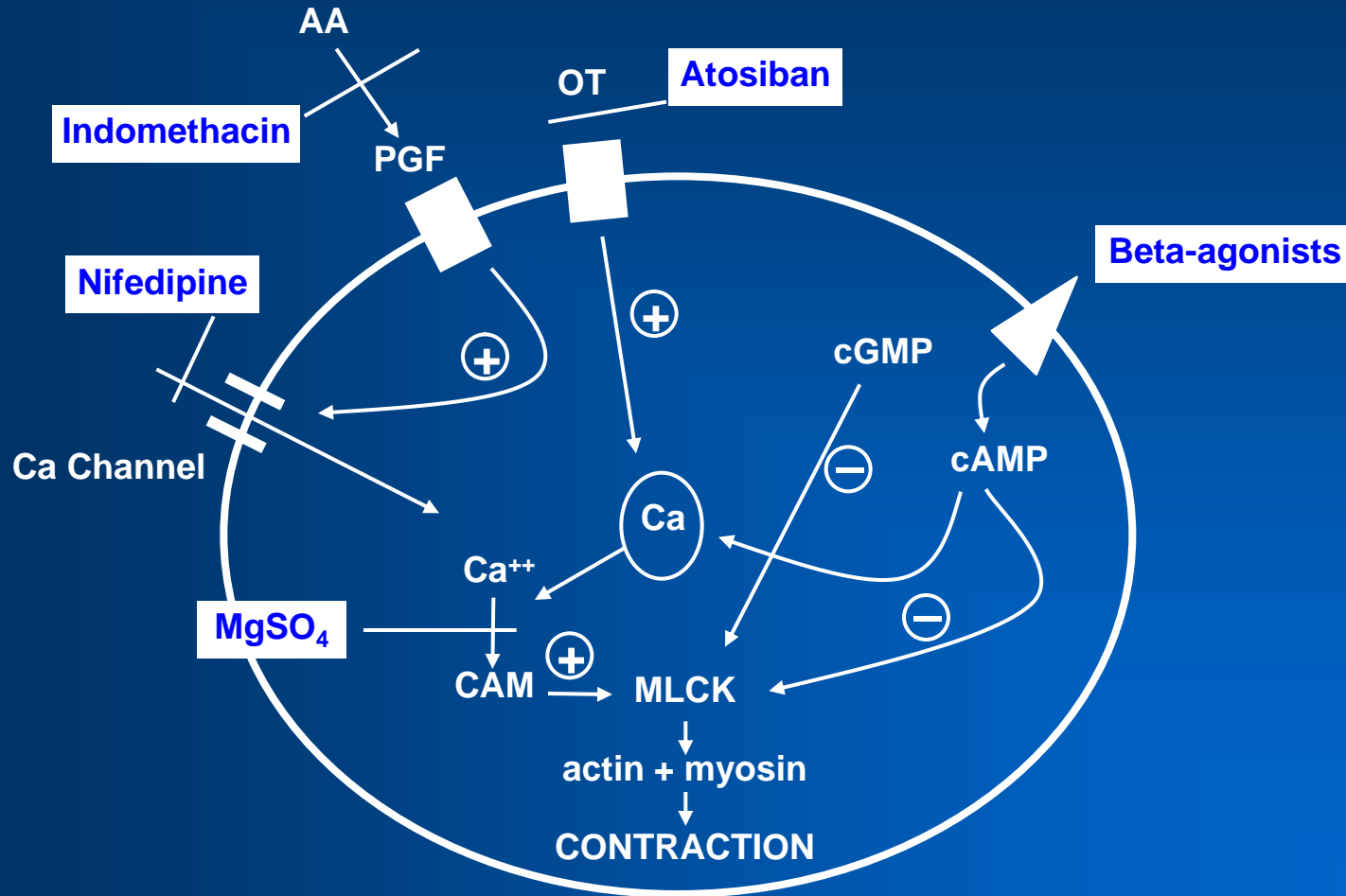
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Nitric Oxide Donors

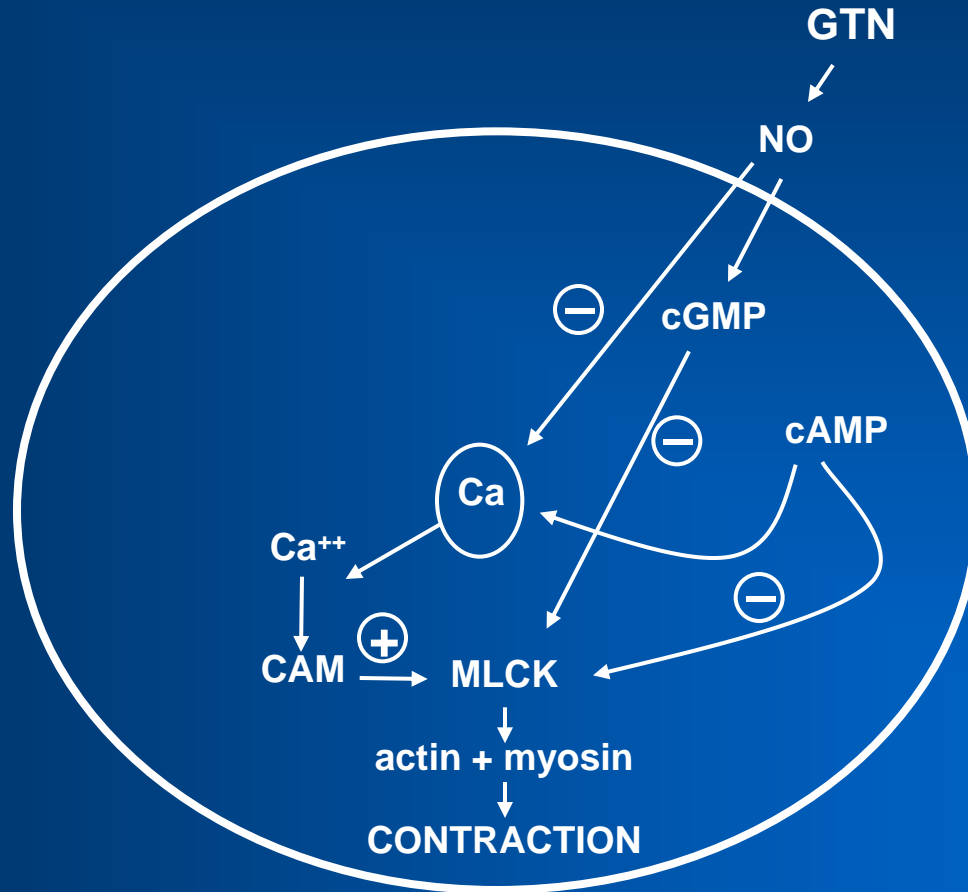
Tocolysis



Nitric Oxide Donors

- Glycerol trinitrate (GTN); Nitroglycerine
- Vasodilator
- Potent smooth muscle relaxant
- Maternal adverse effects
 - headache
 - dizziness
 - hypotension
 - palpitations

Nitric Oxide Donors



Nitric Oxide Donor vs β -mimetic

Bisits *AJOG* 1998;178:862-6

- Single centre RCT, Newcastle, Australia
- 26 women in PTL
 - 24-34 wks, cervix < 5cm
- GTN 10mg patch vs IV albuterol
- No advantage in prolonging pregnancy
- ↓ side effects with GTN

Nitroglycerine vs Magnesium Sulfate

El-Sayed *Obstet Gynecol* 1999;93:79-83

- Single centre RCT, Stanford, California, USA
- 30 women in PTL
 - <35 wks, cervical change or PROM
- IV nitroglycerine vs IV MgSO₄
- ↑ tocolytic failure (63% vs 21%)
- ↑ maternal hemodynamic effects (22% vs 8%)
- ↓ side effects

Nitric Oxide Donor vs Placebo

Smith GN *AJOG* 1999;106:736-9

- Single centre RCT, Kingston, Canada
- 33 women in PTL
 - 24-34 wks, intact membranes
- GTN transdermal patch vs placebo
- No difference in prolonging pregnancy >48 h
- ↑ headaches with GTN

Nitric Oxide Donor vs β -mimetic

Lees *Obstet Gynecol* 1999;94:403-8

- International multicentre RCT, London, UK
- 245 women in PTL
 - 24-36 wks, intact membranes
- GTN 10mg transdermal patch vs IV ritodrine
- No difference in time to delivery
- ↓ preterm births <37 wks (37% vs 48%) NS

Nitric Oxide Donor vs β -mimetic

Wani *Int J Gynecol Obstet* 2004;85:165-7

- Single centre RCT, Abu Dhabi, UAE
- 132 women in PTL
 - 23-34 wks, intact membranes
- 10mg GTN patch vs IV ritodrine
- GTN prolonged pregnancy >14 days, >34 wks, >37 wks (RR 1.23-1.49 95%CI 1.02-1.98)
- ↓ LBW (<2500 gm) [RR 0.44 95%CI 0.26-0.75]

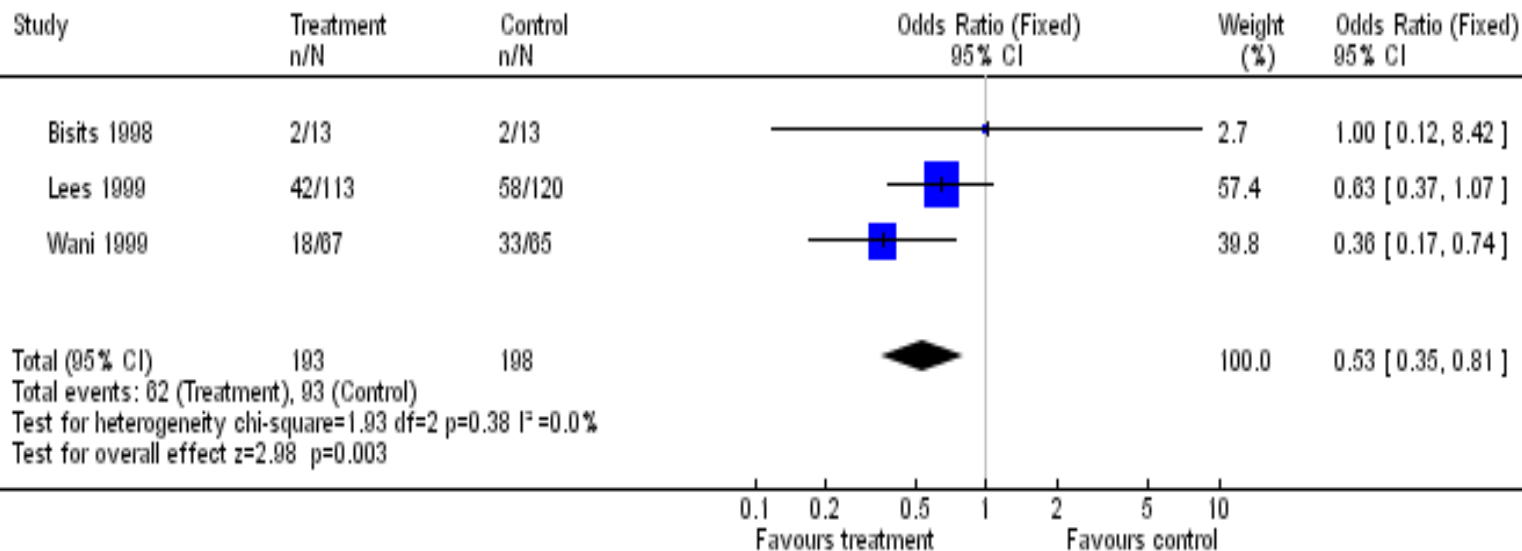
Cochrane Systematic Review

- 5 RCTs (466 women)
- GTN vs other tocolytic or placebo
- No delay in time to delivery
- No improvement in neonatal outcome
- ↓ preterm births < 37 wks compared to other tocolytics (RR 0.69, 95%CI 0.53-0.88)
- ↑ headaches (RR 3.36, 95%CI 1.29-8.76)
- ↓ maternal side effects (RR 0.47, 95%CI 0.37-0.61)

Conclusion: Further RCTs required to assess effectiveness and harm of NO donors

Cochrane Systematic Review

Review: Nitric oxide donors for the treatment of preterm labour
 Comparison: 02 Nitric oxide donors versus any other tocolytic agent
 Outcome: 06 Delivery prior to 37 completed weeks



Nitric Oxide Donor vs β -mimetic

- **Bisits** *AJOG 2004;191:683-90*
- International, multicentre RCT, Australasia (RNOTT)
- 238 women with threatened PTL
 - 24-35 wks, +fFN or PROM
- Transderm 50-mg Nitro patch vs ritodrine/salbutamol
- No difference in time to deliver
- No difference in neonatal outcome
- 35% required rescue treatment with β -mimetic

Neonatal Neurodevelopment following GTN Tocolysis

- RNOTT 18 month follow up
- 156 infants (81 GTN; 75 β -mimetic)
- Physical and psychomotor assessment
 - Griffiths Mental Development Scales
- No difference in psychomotor performance between groups

Nitroglycerine vs Placebo

Smith GN *AJOG* 2007;196:37e1-37e8

- National multicentre RCT, Canada
- 153 women in PTL (Sample size 600)
- Transdermal nitroglycerine vs placebo patch
- Composite perinatal outcome:
 - Perinatal mortality
 - Chronic lung disease
 - Necrotizing enterocolitis
 - IVH (Grade 3 or 4)
 - Periventricular leukomalacia

Nitroglycerine vs Placebo



- Decreased perinatal morbidity
[RR 0.29 95%CI 0.09-1.0](NNT=10)
- ↑ Mean GA at delivery ($p = .04$)
- ↑ prolongation of pregnancy if randomized
< 28 wks ($p = .007$)
- Increased maternal side effects
(RR 1.41 95% CI 1.06-1.86)

Implications for Practice

- Conflicting evidence regarding tocolytic effectiveness of nitric oxide donors
- Important findings of Canadian Preterm Labour Nitroglycerine Trial
- Further investigation required?