

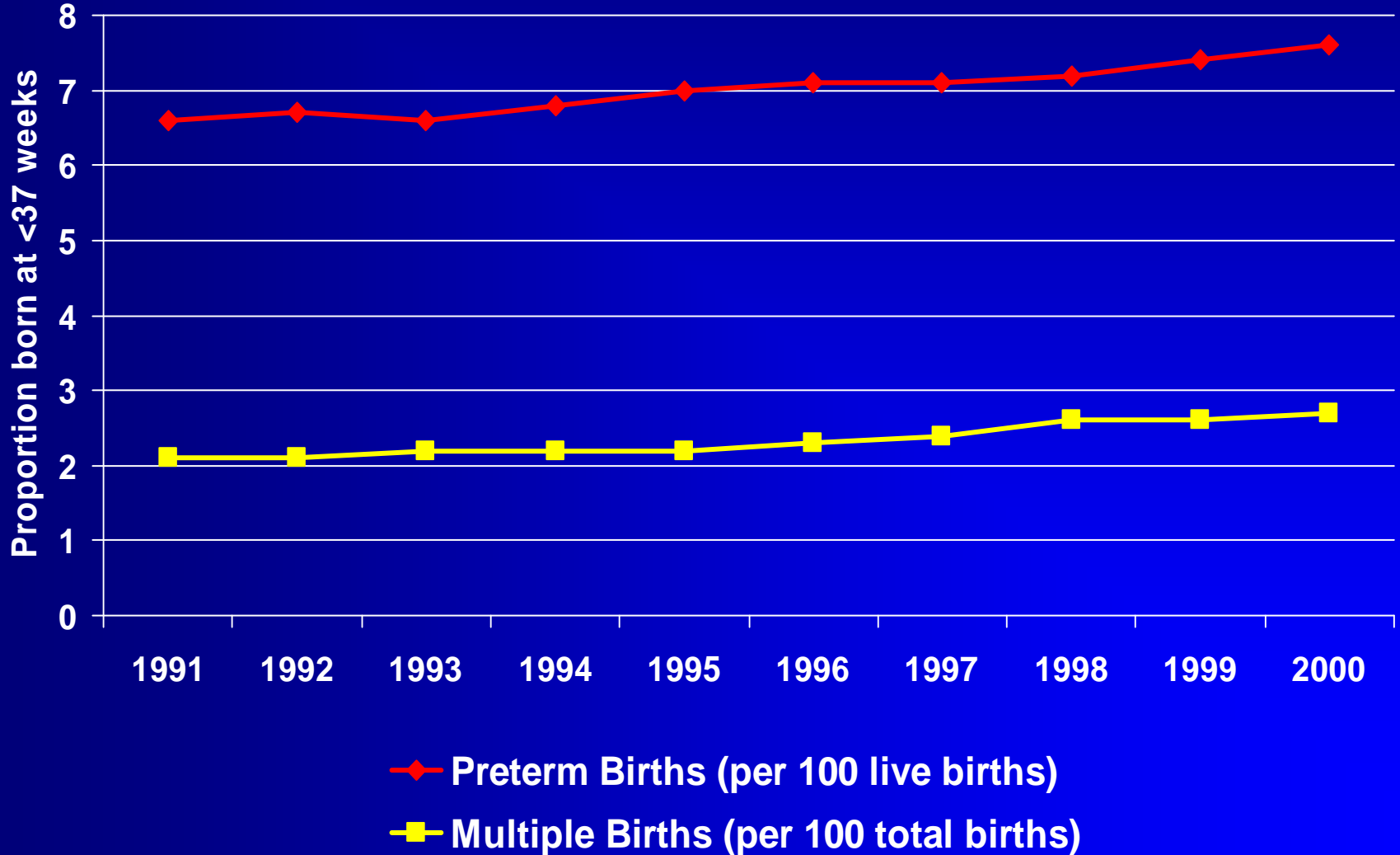
Progesterone to Prevent Preterm Birth



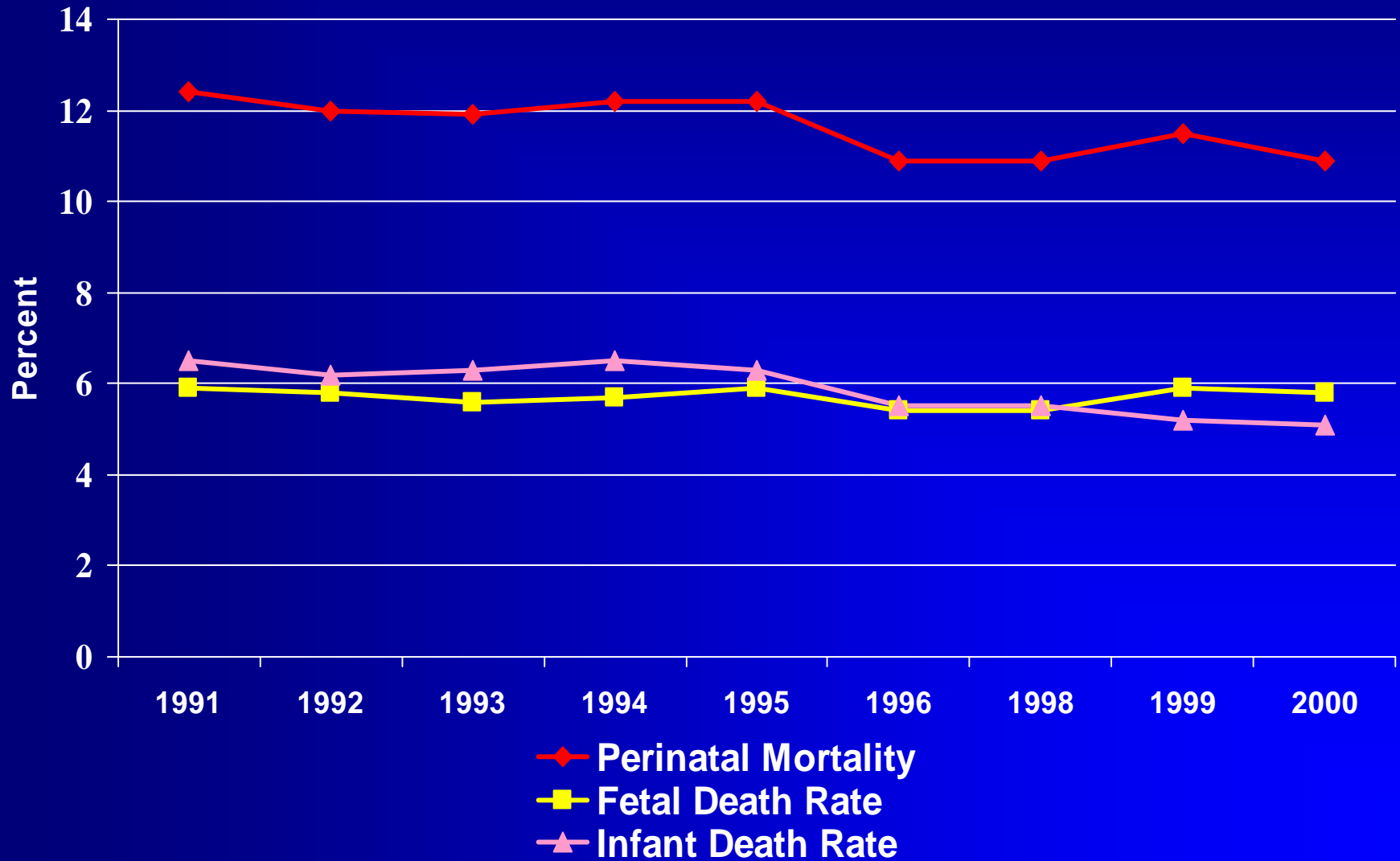
B Anthony Armson MD, MSc



Preterm Birth Rates in Canada

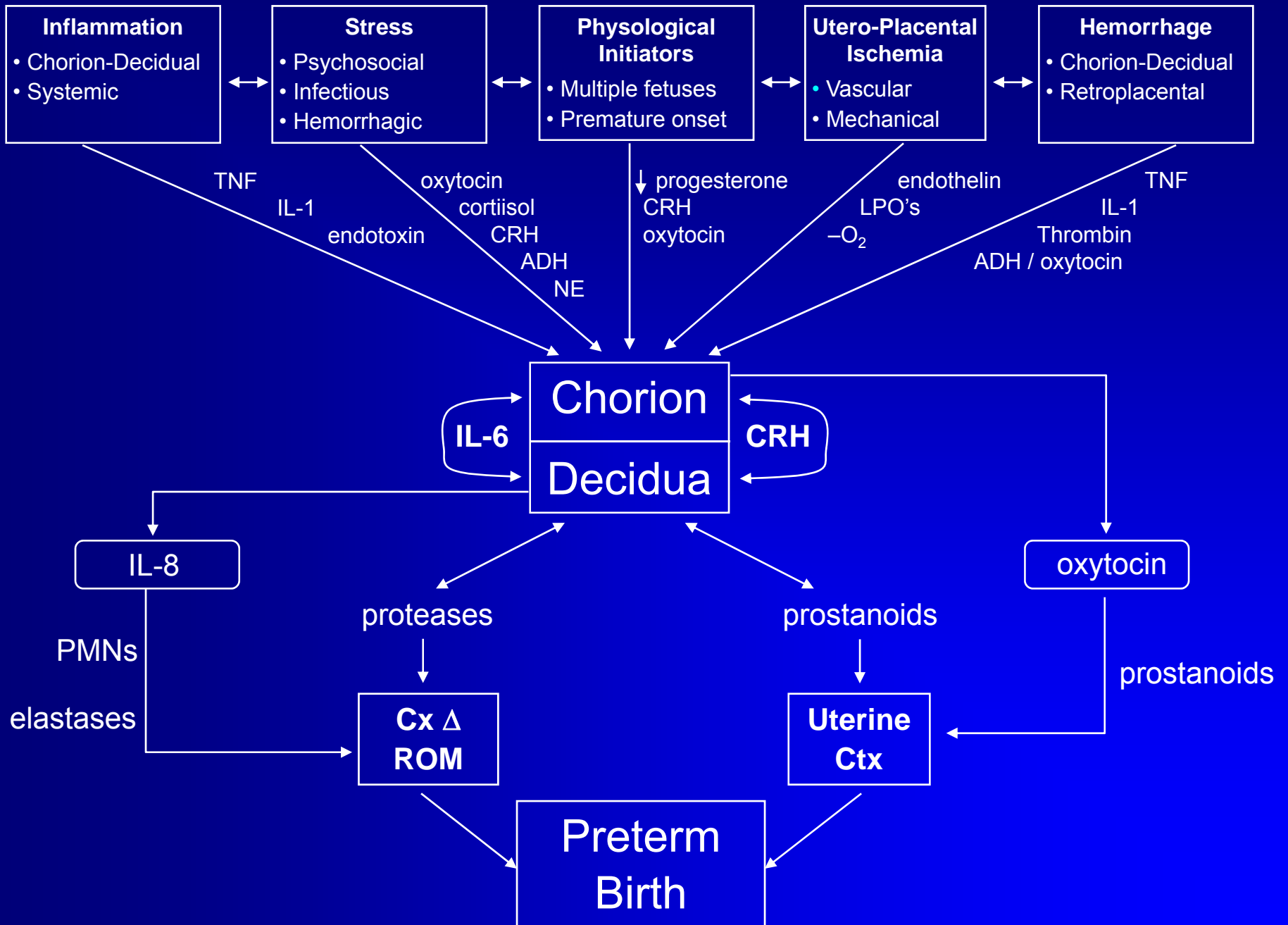


Perinatal Mortality Rate



Spontaneous Preterm Birth

- Preceded by preterm labour or PROM
- 2/3 of all preterm births
- Multiple demographic and obstetric risk factors
 - prior preterm birth
 - low socioeconomic status
 - multiple gestation
 - uterine anomalies
 - short cervical length



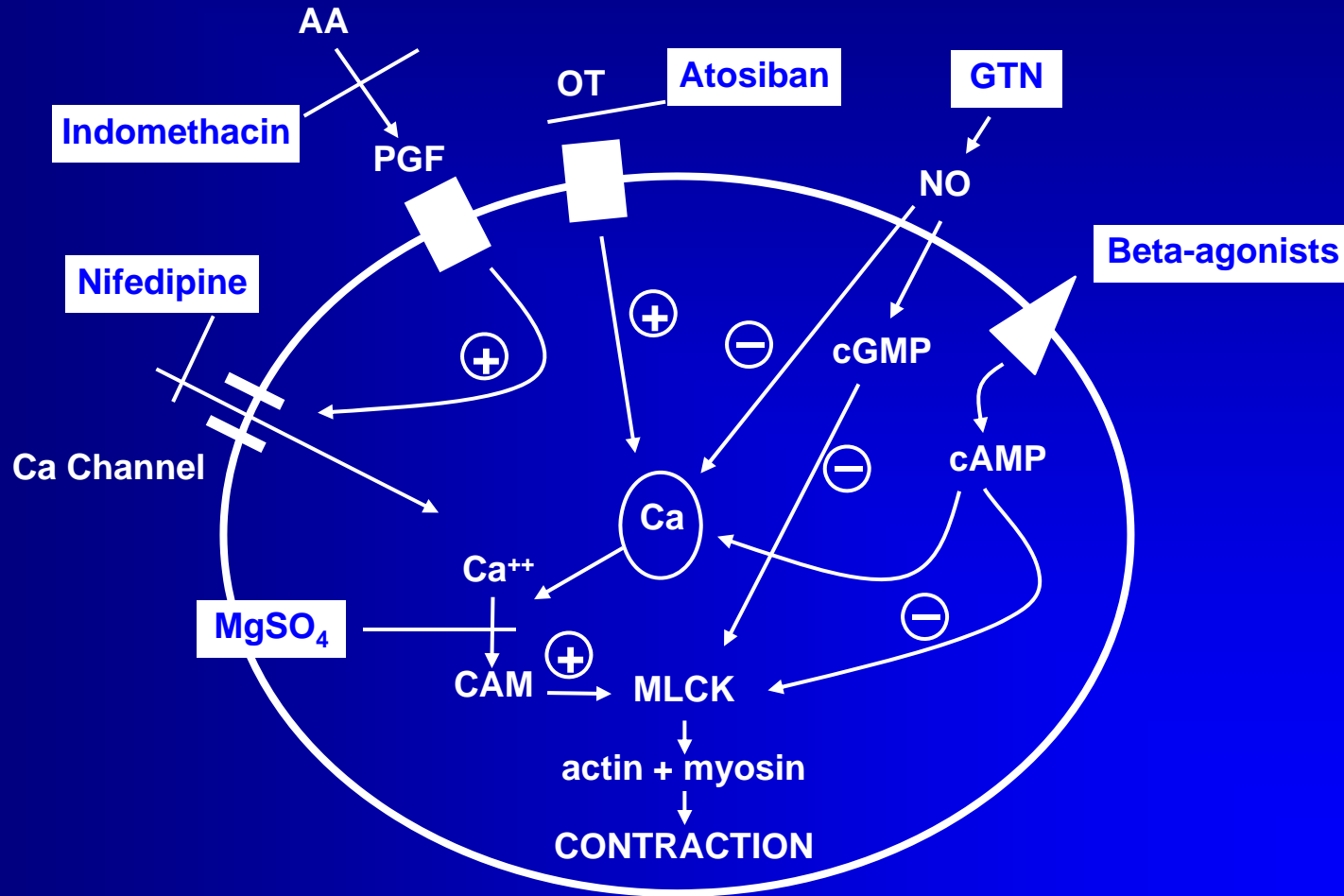
Preterm Birth Prevention

Primary: population-based strategies

Secondary: interventions in high-risk pregnancies

Tertiary: management of preterm labour

Tocolysis



Secondary Prevention Strategies

Education about PTL

No benefit

Bed rest: in hospital

No benefit

at home

Not evaluated

Activity Restriction

? Beneficial for high-risk
occupations

Secondary Prevention Strategies

Cervical Examination No benefit

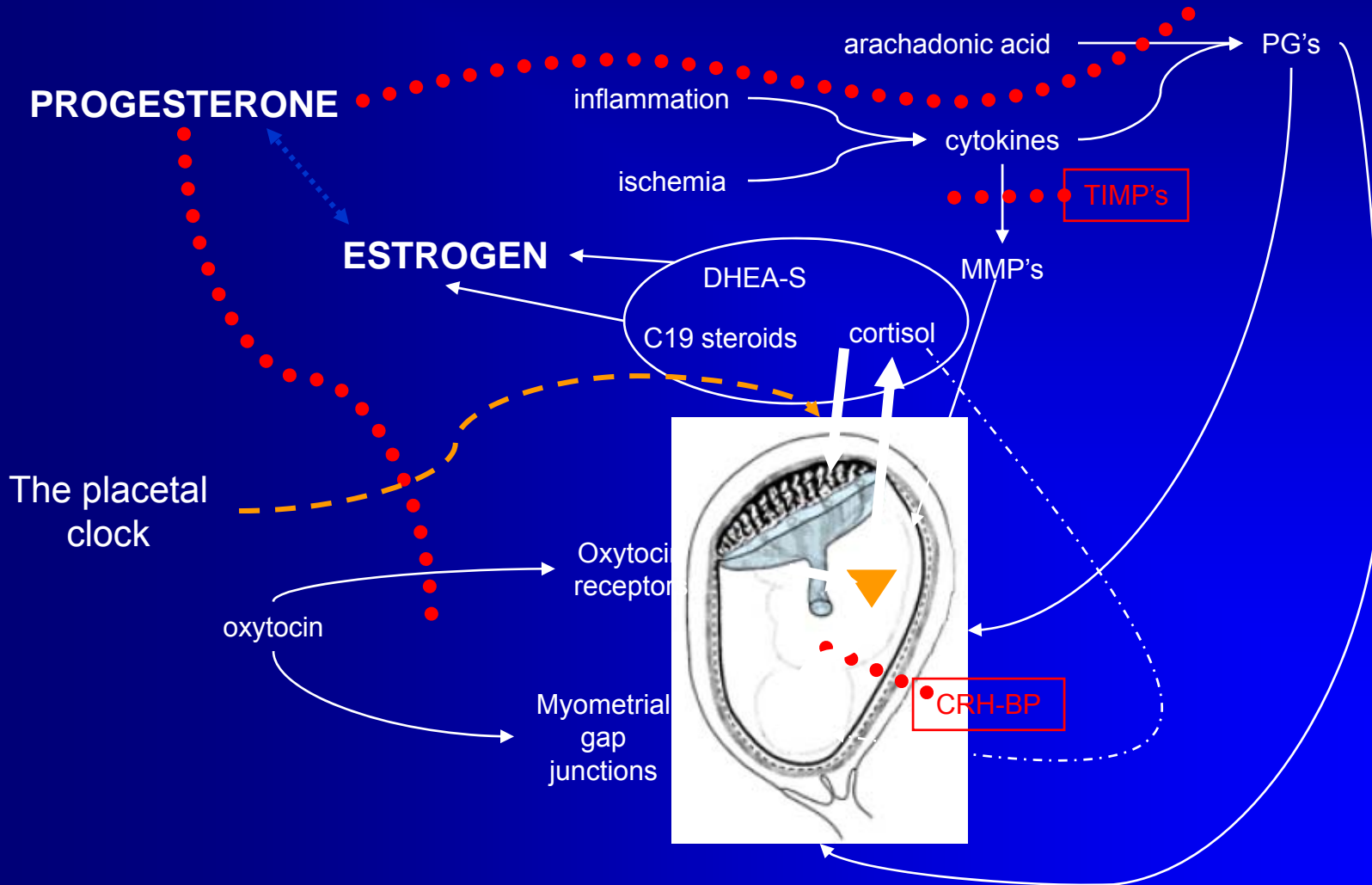
Antibiotic Therapy

- intact membranes No benefit

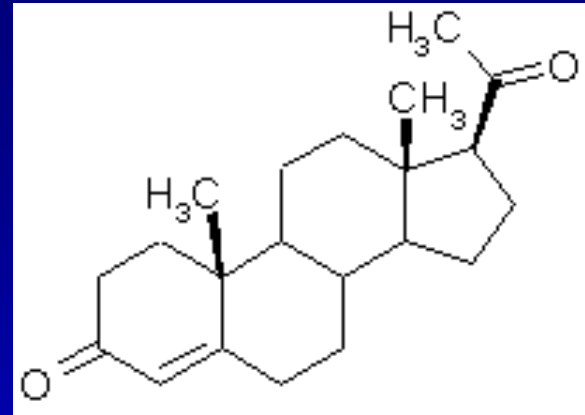
- preterm PROM Beneficial

Cervical Cerclage No benefit

Simplified Schema of the Onset of Labour



Progesterone



- Produced by corpus luteum and placenta
- Maintains pregnancy early in gestation
- Suppresses uterine smooth muscle activity
- Suppresses calcium-calmodulin-light chain kinase system → ↓ calcium influx

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 (17α -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

Progesterone to Prevent Preterm Birth

Study (year)	Population (P/C)	Treatment (weeks)	Preterm Birth Rate(%)	
			Progesterone	Control
Papiernik (1970)	HR (99/99)	28 → 32	4	18
Johnson (1975)	HR (18/22)	→ 37	0	41
Hartikainen- Sorri (1980)	Twins (39/38)	28/33 → 37	31	24
Yemini (1985)	HR (39/40)	→ 37	16	38

Vaginal Progesterone RCT

- Women at high risk for PTB
 - Prior spontaneous PTB
 - Cervical cerclage
 - Uterine anomaly
- RCT : Progesterone(72) vs placebo(70)
- Daily vaginal supp (100g) from 24-34 wks
- Uterine activity 24% vs 54%
- PTB <37 wk 14% vs 29%
 <34 wk 3% vs 19%

NICHD RCT

- Women with prior spontaneous PTB
- Multicentre RCT – 2:1 ratio
- Weekly IM 250mg progesterone(310) vs placebo(153)
 - 16 – 20 wks → 36 wks
- PTB <37 wk 36% vs 55%
- <35 wk 21% vs 31%
- <32 wk 11% vs 20%

Perinatal Outcomes: NICHD Trial

	17P N=306	Placebo N=153	Relative Risk (95% CI)
Preterm birth <37 weeks	111(36.3%)	84(54.9%)	0.66(0.54, 0.81)
Preterm birth <32 weeks	35(11.4%)	30(19.6%)	0.58(0.37, 0.91)
Respiratory distress syndrome	29(9.5%)	23(15.1%)	0.63(0.38, 1.05)
Necrotizing enterocolitis	0	4(2.6%)	NA
Retinopathy of prematurity	5(1.6%)	5(3.3%)	0.50(0.15, 1.70)
Proven sepsis	9(3.0%)	4(2.6%)	1.12(0.35, 3.58)
IVH grade III or IV	2(0.7%)	0	NA
Fetal death	6(2.0%)	2(1.3%)	1.5(0.31, 7.34)
Neonatal death	8(2.6%)	9(5.9%)	0.44(0.17, 1.13)

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

Meta-Analysis of RCTs

- 10 RCTs included (1,339 subjects)
- ↓ PTB (26% vs 36%)
- ↓ LBW (OR 0.50, 95% CI 0.36-0.71)
- No differences in admission for threatened PTL
- No differences in perinatal mortality

Sanchez-Ramos, Am J Obstet Gynecol 2005; 105:273-9

Cochrane Systematic Review

- 6 RCTs (988 women)
- ↓ PTB (RR 0.65, 95% CI 0.54-0.79)
- ↓ LBW (RR 0.63, 95% CI 0.49-0.81)
- ↓ IVH (RR 0.25, 95% CI 0.08-0.82)*

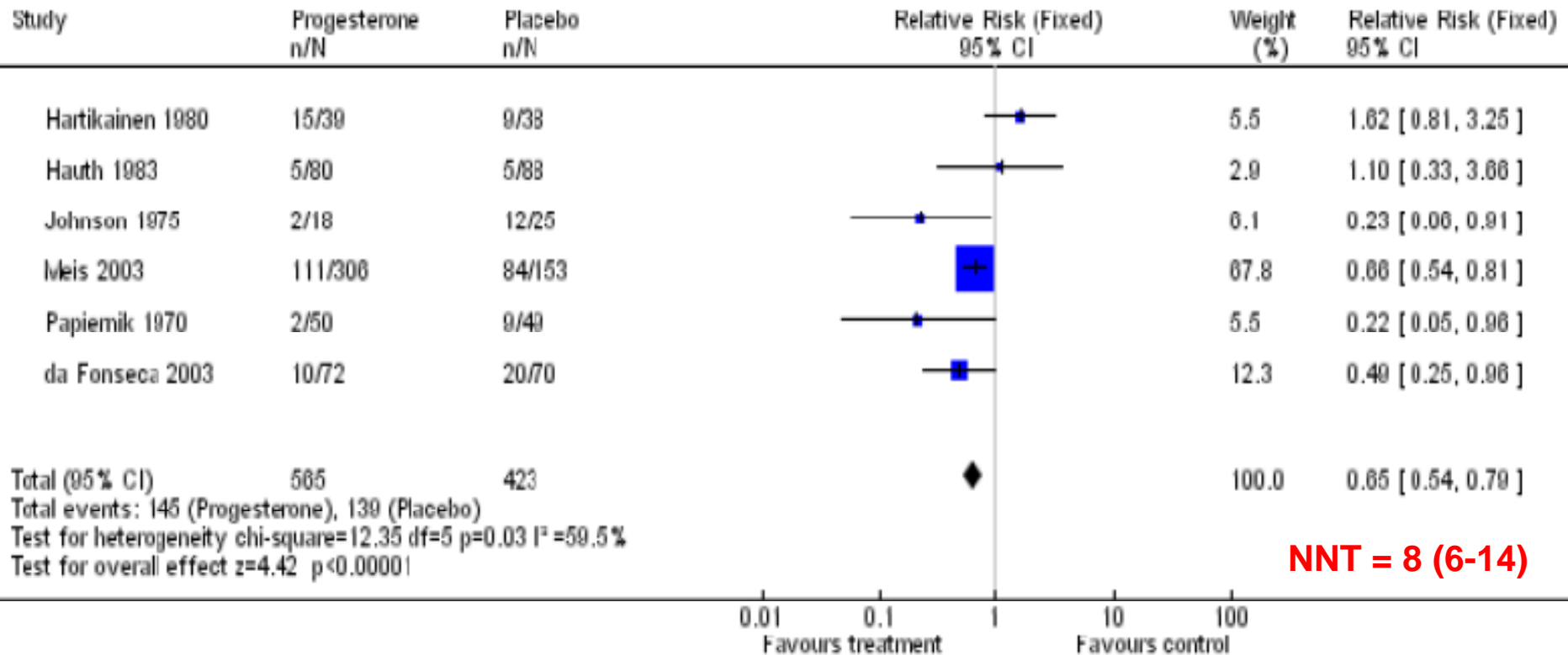
Conclusion: Further RCTs required to assess
benefits and harms of
progesterone therapy.

Preterm Birth < 37 wks

Review: Prenatal administration of progesterone for preventing preterm birth

Comparison: 01 Progesterone versus placebo (all studies)

Outcome: 02 Preterm birth less than 37 weeks



Systematic Review and Meta-Analysis

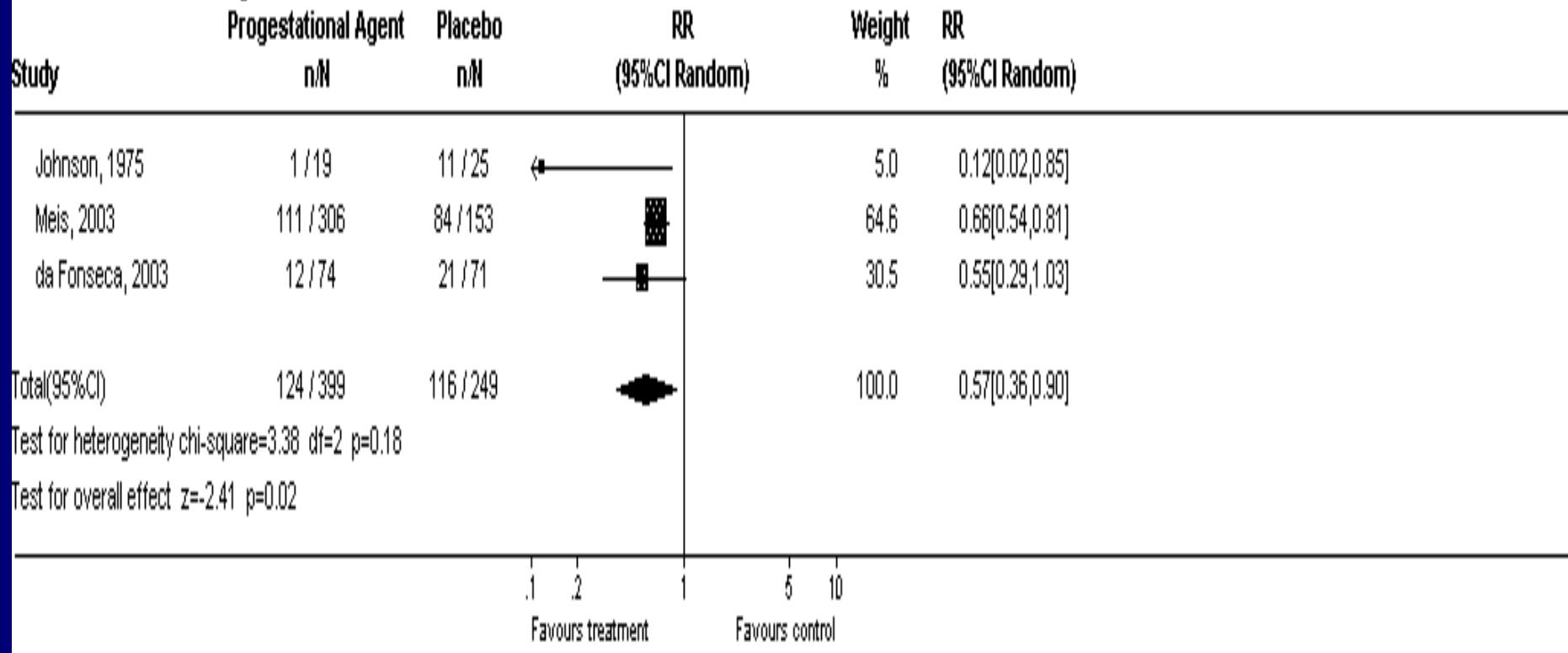
- Progesterone initiated in second trimester
- 3 RCTs (648 women)
- ↓ PTB (RR 0.57, 95% CI 0.36-0.90)
- No effect on perinatal mortality or serious neonatal morbidity

Conclusion: Larger RCTs required to determine effect of progesterone prophylaxis on perinatal outcomes.

Preterm Birth < 37 wks

Comparison: 01 Progesterational agents vs placebo

Outcome: 01 Delivery before 37 weeks



Progesterone Trials

Trial/Country	Selection Criteria	Progesterone	Primary Outcome	Sample Size
PROGRESS, Australia	Previous spontaneous preterm birth; singleton or multiple	Vaginal progesterone 100mg/day	Respiratory distress syndrome	984
Copenhagen, Denmark NCT00329914	Twins	Vaginal progesterone 200mg/day	Preterm birth < 34 weeks	750
STOPPITT, UK	Twins	Vaginal progesterone	Preterm birth < 34 weeks	500
Columbia Laboratories, USA NCT00086177	Previous preterm birth; singleton	Vaginal 8% progesterone gel	Preterm birth ≤32 weeks	636
Pilot Study, Calgary, Canada NCT00343265	Twins, Triplets	Vaginal 8% progesterone gel	Gestational age at delivery	200
STTARS, NICHD, USA NCT00099164	Twins; Triplets	17P 250mg/week	Preterm birth < 35 weeks	600 twin pregnancies; 120 triplet pregnancies
Yale University, USA NCT00120640	Symptoms of preterm labour, singleton	17P 250mg/week	Preterm birth <37, <34, <32 weeks	375
American University of Beirut, Lebanon NCT00141908	Twins	17P 250mg/week	Preterm birth < 37 weeks	290
Obstetrix Medical Group, USA NCT00163020	Twins; Triplets	17P 250mg/week	Mortality or serious neonatal morbidity	321
Paris, France NCT00331695	Short cervix	17P 500mg 1-2x/week	Time to delivery	560

POPPI



Prevention Of Problems of Preterm Birth with
Progesterone in Women at Increased Risk

Research Questions

For women at increased risk of spontaneous preterm birth, does vaginal progesterone decrease (or increase) the risk of:

- 1 perinatal mortality or serious neonatal morbidity;
- 2 - preterm birth <34 weeks;
- 3° - preterm birth <37, <32, <28 weeks;
 - gestational age at birth; chorioamnionitis;
 - maternal adverse outcomes

compared to placebo.

Proposed Trial

- Multicentre, double-masked RCT
- Stratification by centre, multifetal pregnancy
- Vaginal progesterone (100 mg) vs placebo
- From 20 to 33 6/7 weeks
- Intention to treat

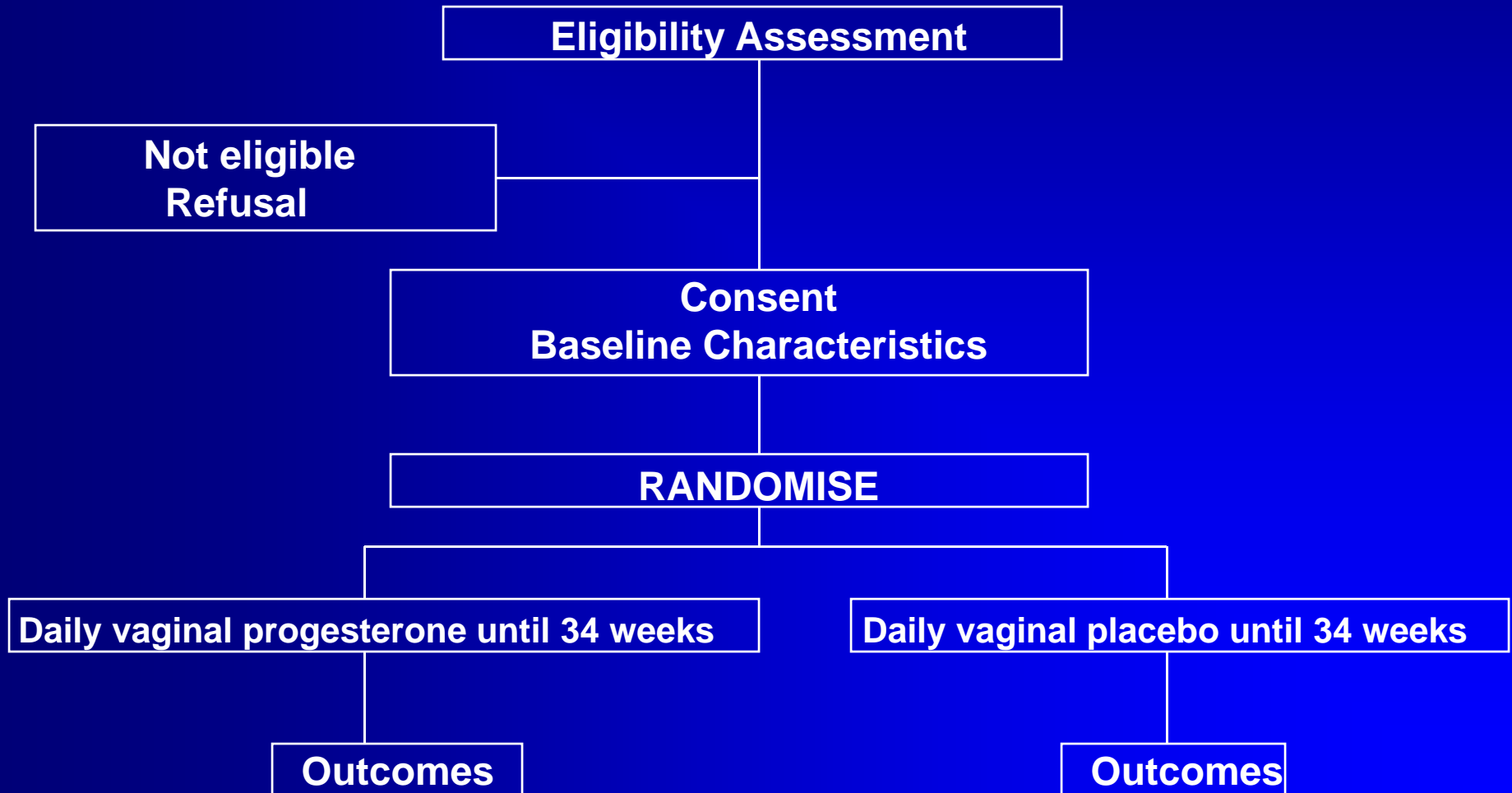
Inclusion Criteria

- 18 0/7 to 23 6/7 weeks
- Increased risk for preterm birth
 - prior spontaneous preterm birth
 - multiple gestation
 - short cervix
 - uterine anomaly
- Fetuses alive at randomization

Exclusion Criteria

1. Risk of primary outcome high
 - Known lethal congenital anomaly
 - Monoamniotic or conjoined twin
2. Contraindication to progesterone treatment
3. Evidence that parturitional process has started
 - ruptured membranes
 - dilated internal os
 - suspected preterm labour
4. Previous participation in POPPI

Study Schema



Primary Outcome

- Fetal or neonatal mortality
- Significant neonatal morbidity
 - RDS
 - Bronchopulmonary dysplasia
 - IVH grade III or IV
 - Cystic periventricular leukomalacia
 - NEC
 - Neonatal infection

Sample Size

- Reduce risk of primary outcome from 9% to 5%
- 80% power, Type I error 0.05%
- 5% loss to follow up
- 740/group, total sample of 1480

Australia/Canada Collaboration

PROGRESS

- Prior singleton <34 weeks
- Vaginal progesterone 100 mg daily
- Primary outcome: RDS
- Sample size: 984(680)

POPPI

- Risk of PTB
- Perinatal mortality/morbidity
- Sample size: 1480(800)



poppi

Prevention Of Problems of Preterm Birth with
Progesterone in Women at Increased Risk