

CHOICE OF TOCOLYTIC AGENTS IN THE MANAGEMENT OF PRETERM LABOUR



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Why predict and prevent preterm delivery?

- 5 – 13% all deliveries
- 75% PNM
- £40,000.00 / infant NICU in the UK
- \$26b acute care/yr in the USA
- Hidden costs:
 - family disruptions*
 - loss of earning*
 - stress*
 - transport to & from hospital*
- Long term morbidity
 - low IQ*
 - neuro-developmental delays*
 - motor deficits*
 - CP, blindness*
 - learning difficulties, special needs*

‘...preterm babies cannot earn enough in their lifetime to offset the cost of their care....’

~ USA Today

- 1 in 5 children with mental retardation
 - 1 in 3 with visual impairment
 - 1 in 2 with cerebral palsy
 - Long term adult risk of MI, stroke, BP
 - Increased risk of DM in adult life
 - Probable increase in cancer risk
-

CHOICE OF TOCOLYTIC AGENT

- **Efficacy (placebo, others)**
 - **Safety (fetal / maternal)**
 - **Neonatal benefits (morbi / mortality)**
 - **Costs (including monitoring)**
 - **Long term data**
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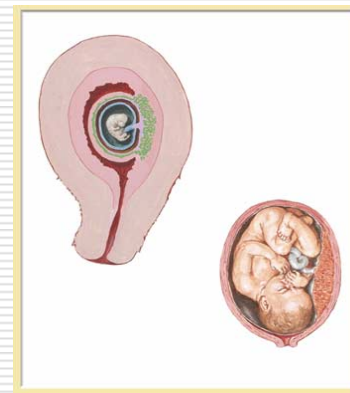
RATIONALE FOR USE OF TOCOLYSIS

TOCOLYSIS PER SE:

- “Does not improve neonatal outcome”
- Maternal morbidity may be high
- D/4 its reasonable not to use

RATIONALE FOR USE:

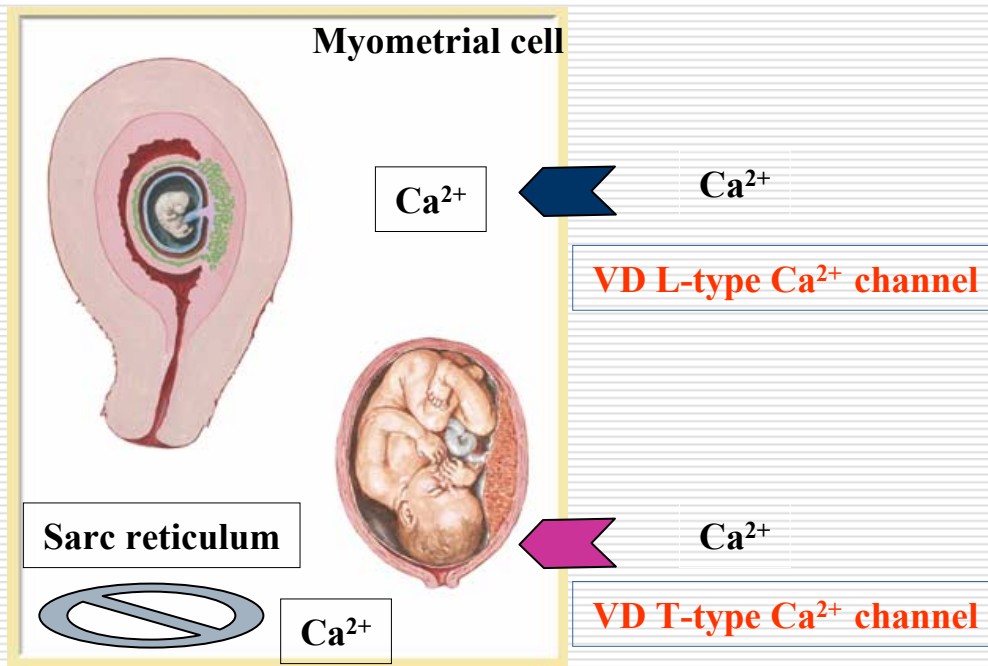
- For in-utero transfers
- To complete doses of corticosteroids
- For early gestation < 32 weeks



CONTRAINDICATED IN:

- advanced labour
 - placental abruption
 - intrauterine infection
 - known sensitivity to agent
-

REGULATION OF MYOMETRIAL CONTRACTILITY

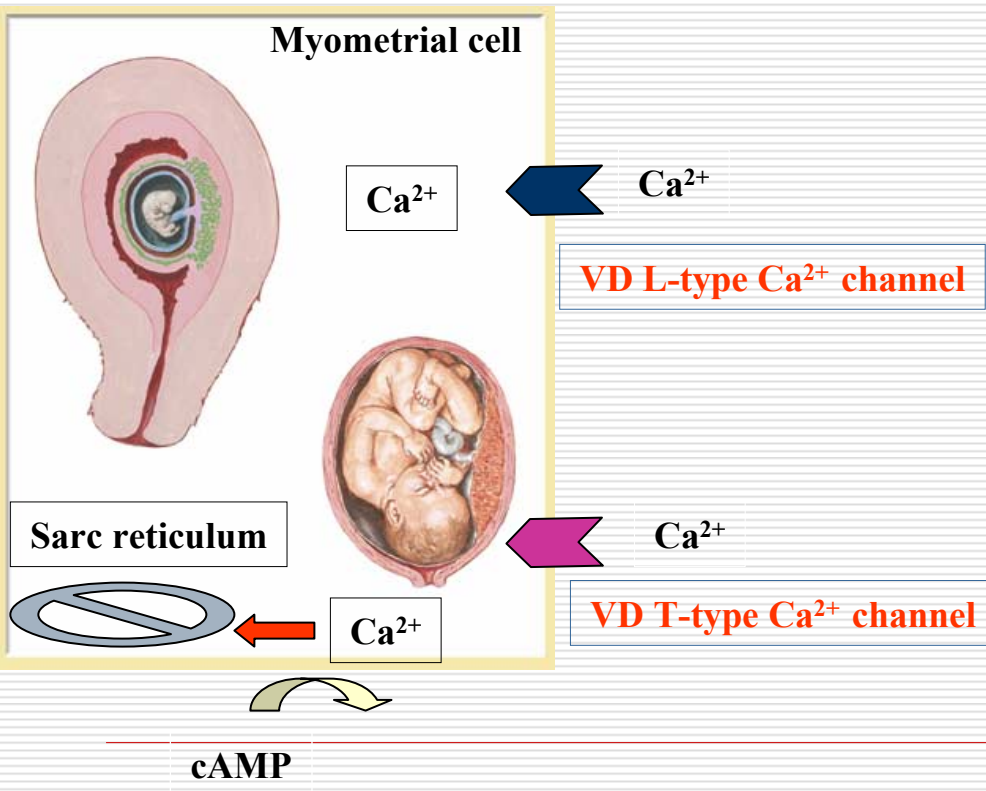


Tocolytics exert their effect by reducing the level of IC Ca^{2+}

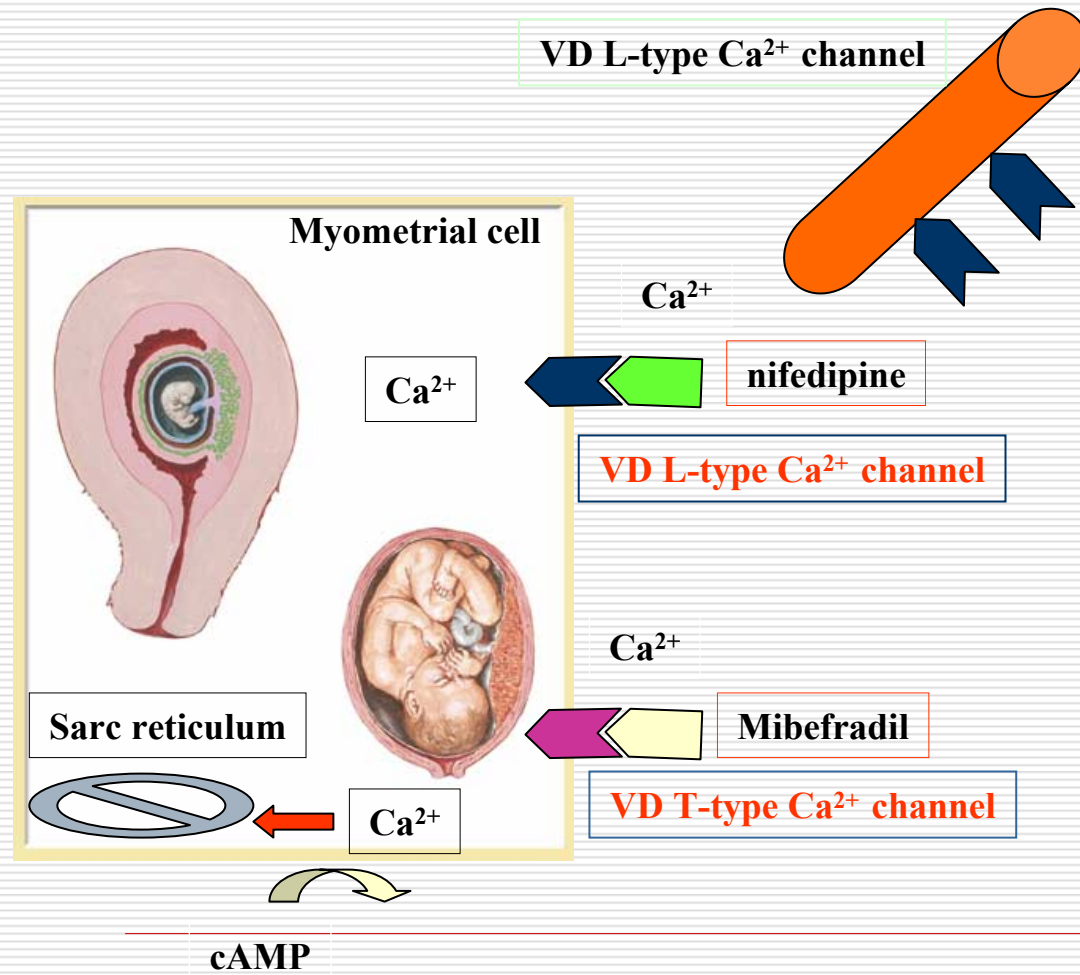
β - AGONISTS (ritodrine, terbutaline, salbutamol)

- Increase cAMP prod
- Uptake of IC Ca^{2+} into SR
- Down regulation - tachyphylaxis
- Postpone delivery 24 – 48hrs
- No sig red in PTB, PNM / M

- ✓ IV-admin. intensive monitoring,
- ✓ Palpitations 48% vs 5% placebo
- ✓ Tremors 30% vs 4%
- ✓ Nausea 20% vs 12%
- ✓ Headaches 23% vs 6%
- ✓ Chest pains 10% vs 1%
- ✓ Pulmonary oedema
- ✓ Death
- ✓ Arrhythmias
- ✓ K^+ , Na^+ disturbances
- ✓ No longer 1st choice agents



Ca²⁺ CHANNEL BLOCKERS (nifedipine, mibefradil)



- closes L-type Ca²⁺ channels
- uterine + vascular smooth muscles
- vasodilation, -ve ino / chronotropic
- compensatory adrenergic drive
- myocardial integrity?
- safety profile under studied
- uterine specific T-channel blocker

- ✓ Oral admin. (30 – 160 mg)
- ✓ Slightly more effective than ritodrine
- ✓ Associated with less RDS
- ✓ Associated with less NICU admissions
- ✓ Fewer maternal side effects

*No evidence of improved neonatal outcome
Headaches*

*? Sudden reductions in uterine blood flow
Not licensed yet for PTL in the UK*

Nifedipine tocolysis associated atrial fibrillation responds to DC cardioversion

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Case report

A 38-year-old woman presented at 33 weeks of gestation with threatened preterm labour. Her obstetric history included two normal vaginal deliveries at term and a miscarriage at 19 weeks, the details of which were not known. She had conceived with a copper intrauterine contraceptive device,

She was reviewed in the antenatal clinic and during the pregnancy she remained asymptomatic. She went into spontaneous labour at 41 weeks of gestation and delivered a male infant weighing 3570 g. She remained asymptomatic through the rest of pregnancy and delivery. Her recovery was uneventful. She has returned to her normal state and has had no further arrhythmias.

subjects with normotension,⁴ but this feature is not absolute and should not be taken for granted. Although the efficacy of nifedipine as a tocolytic agent is well documented, there are no good safety data on its use for tocolysis in pregnant women.

Up to 40% of spontaneous preterm labour is infection driven, although the inflammatory response is not usually evident in the mother. The earlier in gestation the preterm labour, the greater the risk of infection as the driving factor and the greater the pressure for tocolysis. Clinicians should beware that the same inflammatory mediators that modulate the process of infection and preterm labour can potentially alter cardiac function in such a way that any further demand imposed on the myocardium by nifedipine may not be tolerated.

For me, the real lesson of this case is about the critical need to evaluate the potential benefit of tocolysis in every case against the risks and not about the beneficial role of direct current cardioversion for atrial fibrillation induced by an arguably unwarranted nifedipine tocolysis. ■

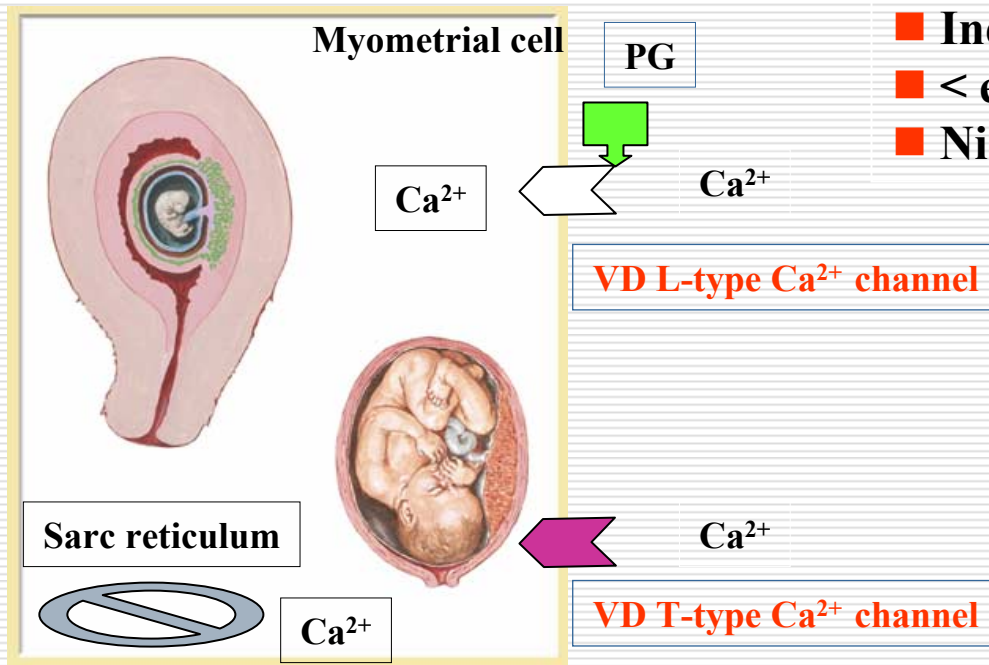
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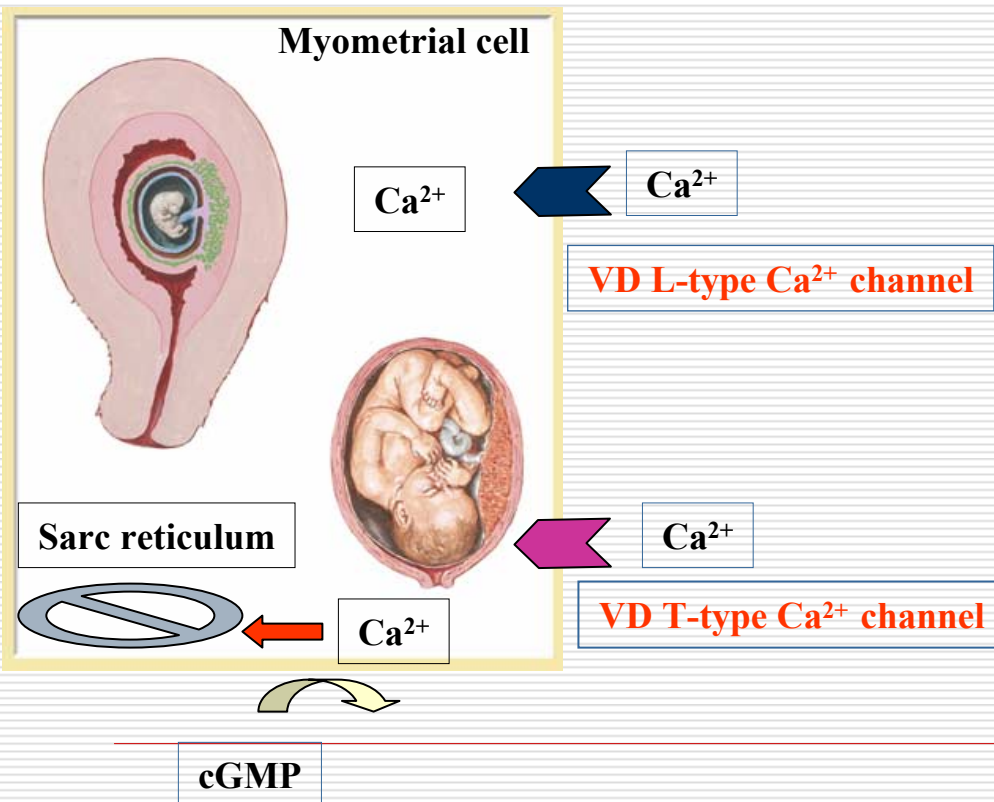
PROSTAGLANDIN INHIBITORS (*indomethacin*)



- PG directly opens Ca²⁺ channel – influx
- COX-1 constitutive, > in fetal CVS
- COX-2 inducible, > membranes + decidua
- Indomethacin is non-specific inhibitor
- < effect b4 30 wks.
- Nimesulide (sp COX 2) – still oligo-

No evidence of superior efficacy
Fewer maternal s/e
Premature closure of the ductus
Renal vaso-constriction
Cerebral vaso-constriction
NEC

NITRIC OXIDE (NO) DONORS *(GTN patch)*



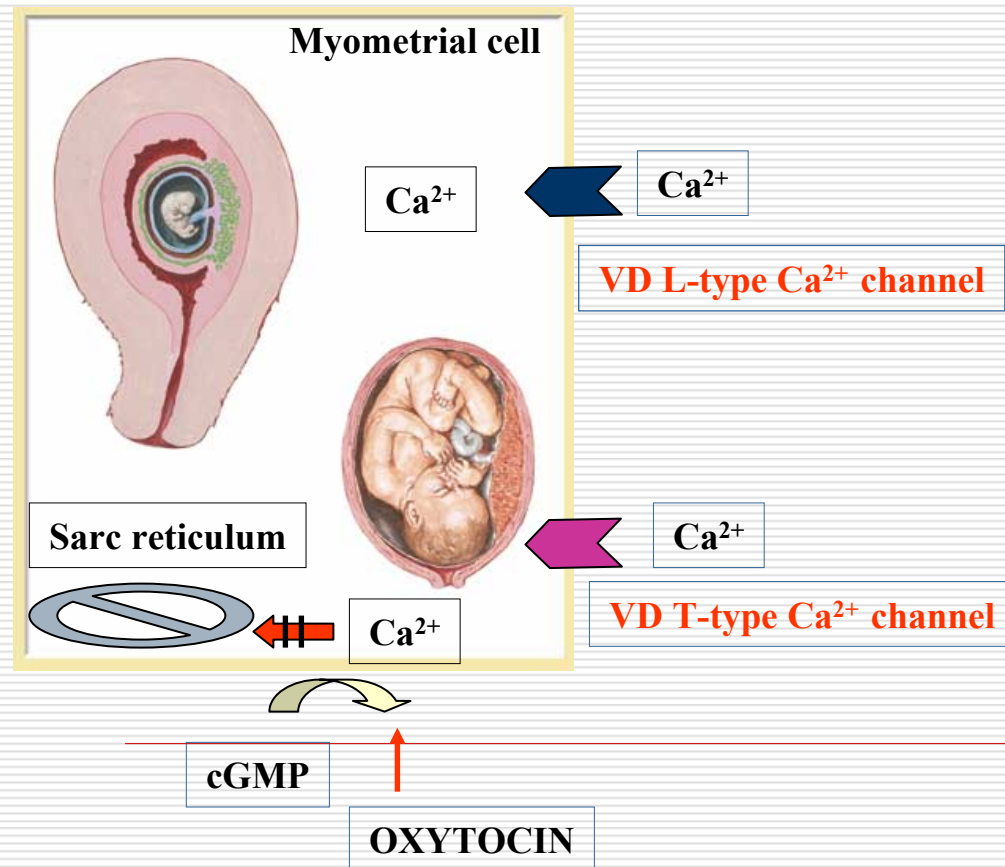
- increase cGMP production
- uptake of IC Ca²⁺ into SR
- powerful smooth m relaxant
- myometrium relatively insensitive
- may also ripen the cervix

administered as patches
comparative studies: too small
few side effects - headaches
larger trials in progress
not licensed for PTL in the UK

OXITOCIN ANTAGONISTS (*ATOSIBAN*)

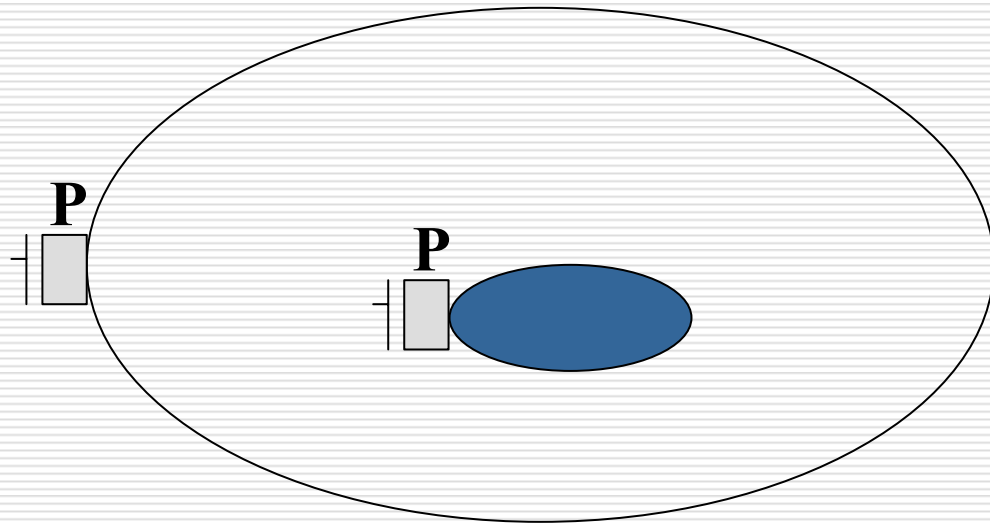
- oxytocin regulate cAMP systems
- increase IC Ca^{2+} release from SR
- OA inhibit Ca^{2+} release from SR
- atosiban specifically antagonises oxy-R

- ❖ equivalent efficacy to β -agonists
- ❖ fewer maternal s/e
- ❖ substantially more expensive
 - £275 / 24 hr; 1680.00 SR
 - £13 ritodrine; 80.00 SR
 - £1.50 nifedipine; 10.00 SR
- ❖ no intensive monitoring
- ❖ licensed for PTL in the UK
- ❖ No data on children exposed in-utero



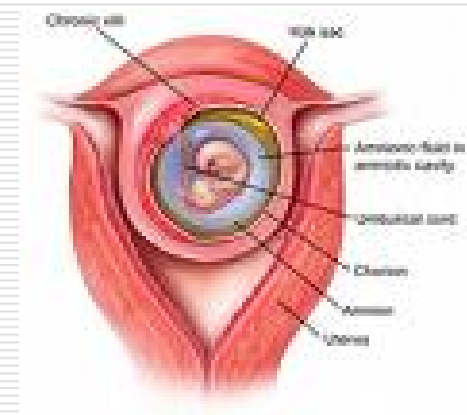
PREVENTION OF PTD ~ USING PROGESTERONE

Genomic or non – genomic effects



Hypothesised modes of action

- ❑ suppresses pro-labour genes
- ❑ decreases conduction of contractions
- ❑ increases threshold for stimulation of a contraction
- ❑ decreases spontaneous activity
- ❑ decreases the number of oxytocin receptors
- ❑ prevents the formation of gap junctions
- ❑ inhibits PG action via PGDH

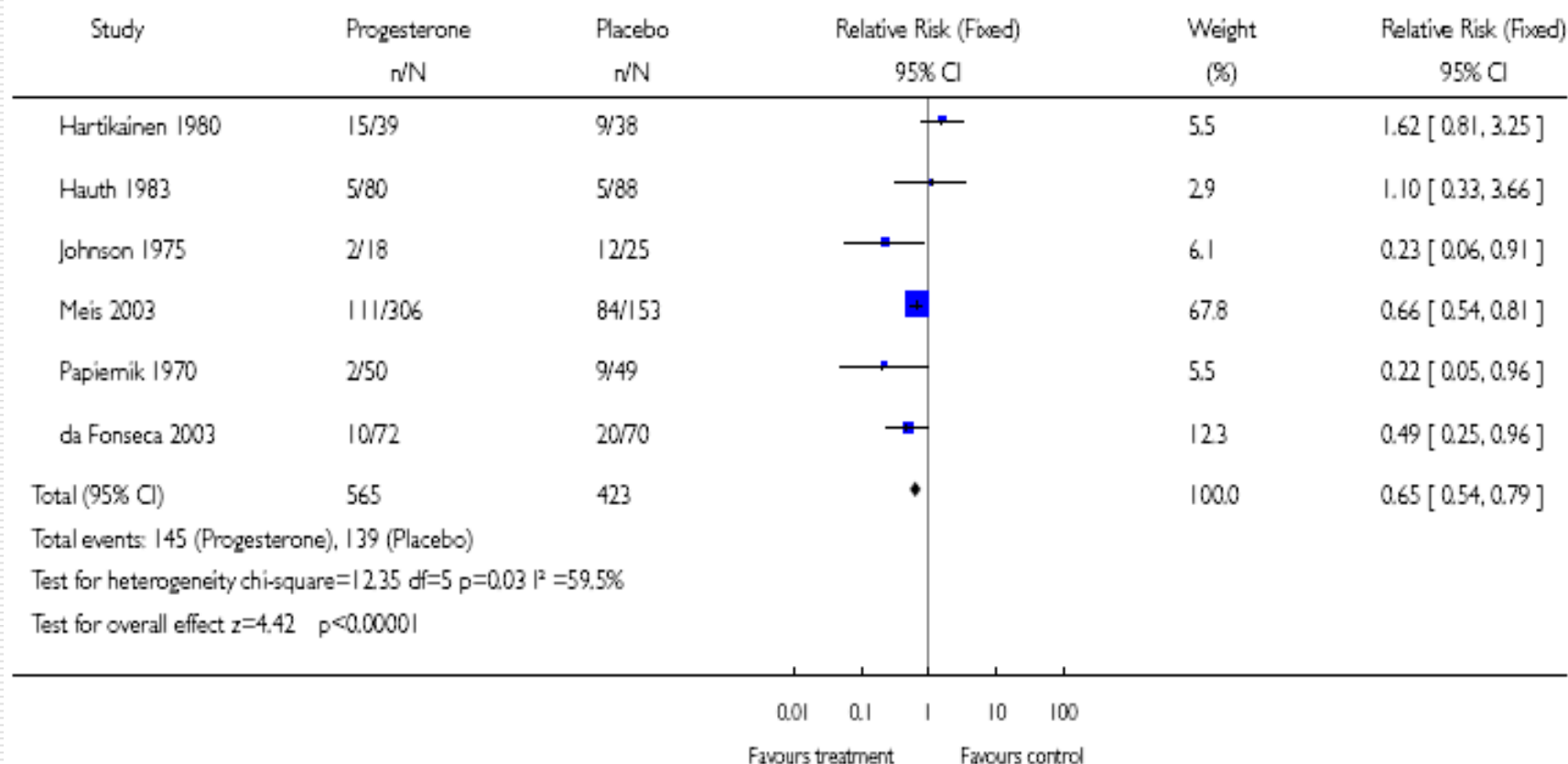


- ❑ anti-progesterone (RU486) causes ripening
- ❑ soft + ripe cervix but no contractions
- ❑ declining progesterone induces inflammation
IL-8, PG, MMP, & NO
- ❑ NF- κ B mediates the effects of IL-1 β & TNF- α
- ❑ NF- κ B opposes the actions of progesterone
- ❑ 17-(OH)P prevents transcription of inflammatory mediators

Review: Prenatal administration of progesterone for preventing preterm birth

Comparison: 01 Progesterone versus placebo (all studies)

Outcome: 02 Preterm birth less than 37 weeks

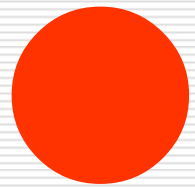


Outstanding issues regarding progesterone therapy

- What is the best mode of administration?
 - What is the optimal dose?
 - What are the maternal side effects?
 - What is the optimal gestation to start therapy?
 - What is the optimal duration of therapy?
 - Does prolongation of pregnancy mean improved long-term health?
-

CONCLUSIONS

- β - agonists no longer 1st choice tocolytics
 - Significant safety concerns on nifedipine
 - Indomethacin assoc with fetal morbidity
 - GTN few data, unlicensed
 - Atosiban expensive but currently recommended
 - MgSO₄, progesterone are alternatives
-



Thank you !!

Size of risk correlates with GA of prior delivery

Study/Trial	Recurrence of sPTB RR (95% CI)	Gestational Age for Recurrence of Preterm Birth
MFMU Network ⁷	2.5 (1.9–3.2)	For initial delivery at less than 37 wk
Missouri ¹⁰	3.6 (3.2–4.0)	For initial delivery at less than 35 wk
Dallas, Texas ⁸	5.9 (4.5–7.0)	For initial delivery at less than 35 wk
Denmark ⁴	4.8 (3.9–6.0)	For initial delivery at 32–36 wk
Denmark ⁴ , MFMU Network ⁷	6.0 (4.1–8.8)	For initial delivery at less than 32 wk
MFMU Network ⁷	10.6 (2.9–38.3)	For initial delivery at less than 28 wk

Risk of PTD based on prior pregnancy outcome

1 st	2 nd	3 rd	RR
Term	4.4 %	-	1.0
PTD	17.2 %	-	3.0
Term	Term	2.6 %	0.6
PTD	Term	5.7 %	1.3
Term	PTD	11.1 %	2.5
PTD	PTD	28.4 %	6.5

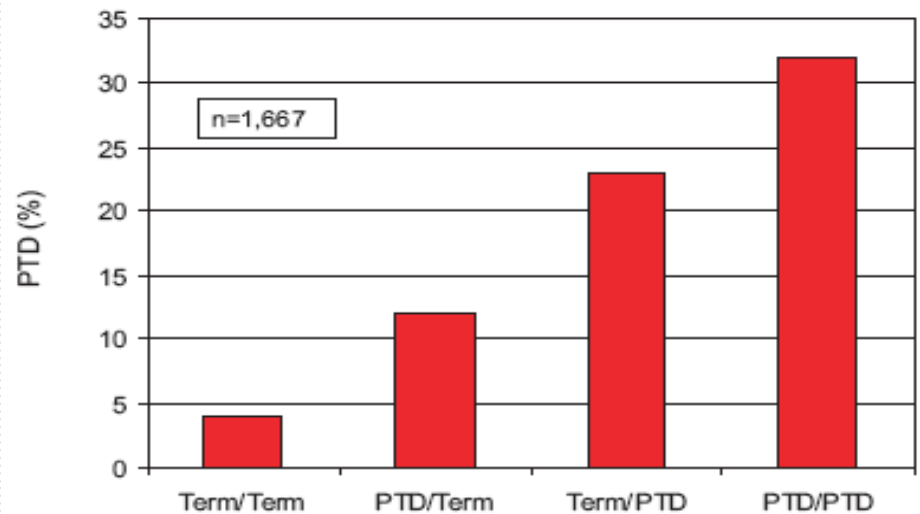
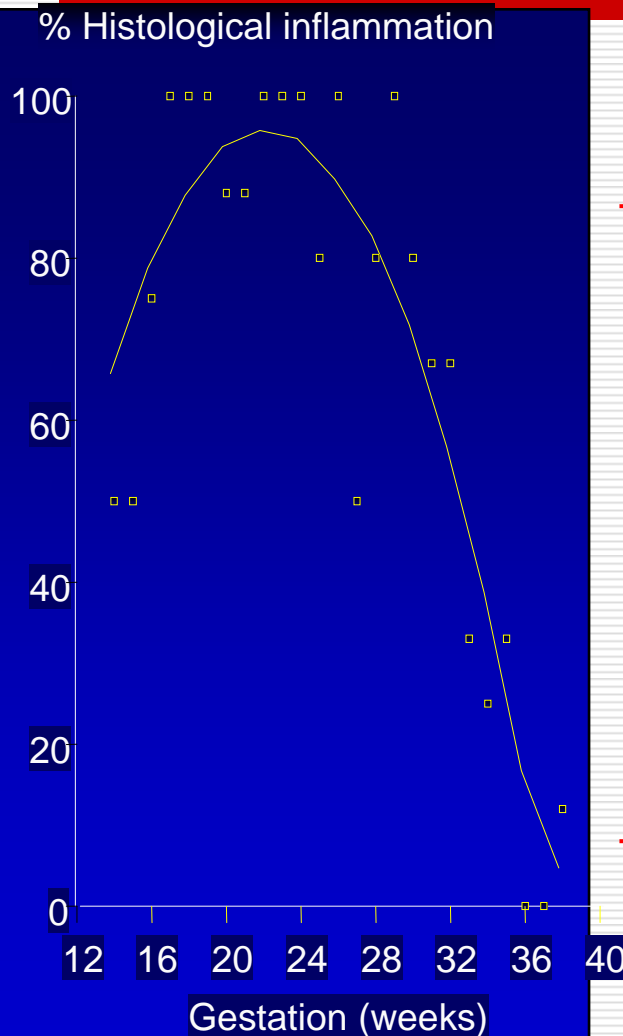


Fig. 4. The risk of subsequent preterm birth is related to the outcome of the prior pregnancy, with the lowest risk occurring when a woman has had two prior term births and the highest risk when she has had two prior preterm births. PTD, preterm delivery. Data from Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. *Br J Obstet Gynaecol* 1985;92: 921-8.

Prevalence at delivery of histologic chorioamnionitis at different stages of gestation

Sebire et al 2001

Chorioamnionitis / choriodecidual inflammation



Weeks of gestation	Histologic CA (n)	Total (n)	Percent (%)
21 – 24	17	18	94.4
25 – 28	19	48	39.6
29 – 32	34	96	35.4
33 – 36	53	497	10.7
37 – 40	233	6139	3.8
41 – 44	36	707	5.1
Total	392	7505	5.2