PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

The clinical pharmacology review and research outcomes - *Progesterone in pregnancy maintenance*

Paul PIETTE, *PharmD*
Senior Research Fellow
Scientific & Medical Affairs
Besins Healthcare
Brussels - Belgium
ppiette@besins-healthcare.com

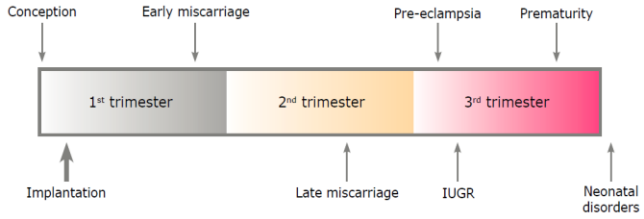
PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

financial disclosure

Paul Piette, PharmD
Scientific & Medical Affair
Consultant for Besins Healthcare Global

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

What is TM and…why progesterone is so important during the all pregnancy…

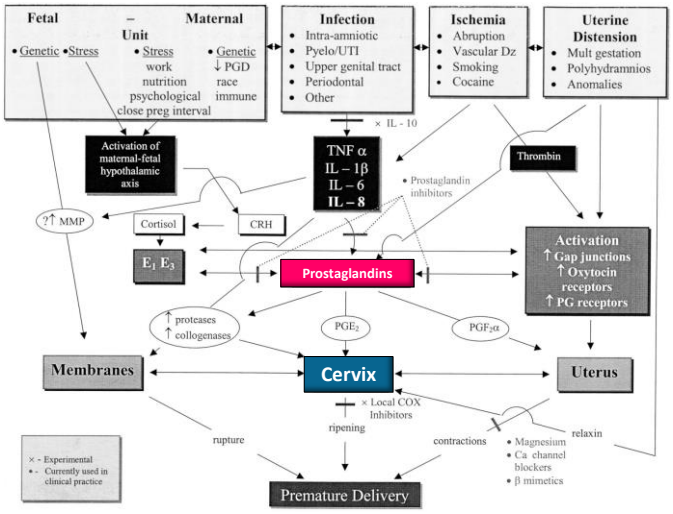


- Miscarriage (M) is spontaneous loss of pregnancy before the fetus has reached viability, from the time of conception until 24 weeks of gestation.[1]
- TM is defined by vaginal bleeding (and pain) in a woman with a confirmed pregnancy.[1]
- Recurrent miscarriage is defined as three or more consecutive pregnancy losses, although many clinicians define it as 2 or more losses.[2]

1. Rai R, Regan L. Lancet 2006; **368**: 601-611.
2. Griebel CP, Halvorsen J, Golemon TB, Day AA. 2005; **72**: 1243-1250

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

ETHIOLOGIC PATHWAYS leading to Preterm Birth



Rodts-Palenik et al. *Obstet Gynecol Survey 2002;* **57 (5)***: S9 – S34*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Role of progesterone in prevention of preterm birth

Mechanism of action

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

MYOMETRIAL RELAXATION AND CONTRACTION

- Progesterone induces high levels of cyclic Adenosine Mono Phosphate and time-dependent stimulation of Nitric Oxide Synthetase (NOS) [1]
- Progesterone inhibits formation of myometrial gap junctions (channels made of connexin 43) [2]
- Progesterone and its metabolites induce uterine quiescence through interactions between nuclear and membrane progesterone receptors [3,4,5]
- Progesterone maintains low levels of prostaglandins (via cyclooxygenase), oxytocin and intracellular calcium

1. **Khorram O et al.** *Fertil Steril 2009;* **91***: 2157-62*
2. **Garfield RE et al.** *Am J Physiol 1980;* **238***: C81-9*
3. **Perusquía M et al**. *Life Sci 2001;* **68***: 2933-44*
4. **Karteris E et al**. *Mol Endocrinol 2006;* **20***: 1519-34*
5. **Merlino AA et al**. *J Clin Endocrinol Metab 2007; 92: 1927-33*

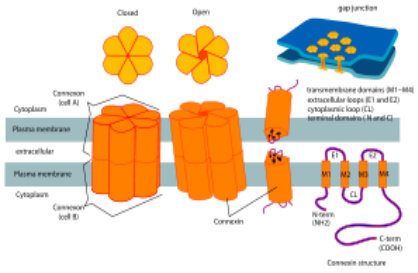
PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

MENACE OF PRETERM DELIVERY
Mechanism of action

- Progesterone inhibits inflammatory responses associated with preterm parturition
- Progesterone promotes myometrial relaxation

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

ROLE OF GAP JUNCTION

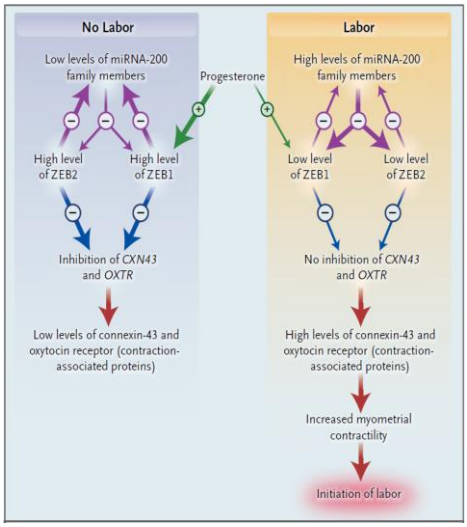


- **Connexin 26**
  - ✓ High during pregnancy
  - ✓ ↓ onset of labor
- **Connexin 43 (45 – 40)**
  - ✓ Low during pregnancy
  - ✓ ↑ immediately before the onset of labor

Pierce et al. *Am J Obstet Gynecol 2002;* **186 (3)***: 504-11*
Cluff et al. *Reprod Biol Endocrinol 2006;* **44***: 24*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

How does Progesterone relax the Uterus in Pregnancy?



Zakar T et al. *N Engl J Med 2011; 364(10): 972-973*

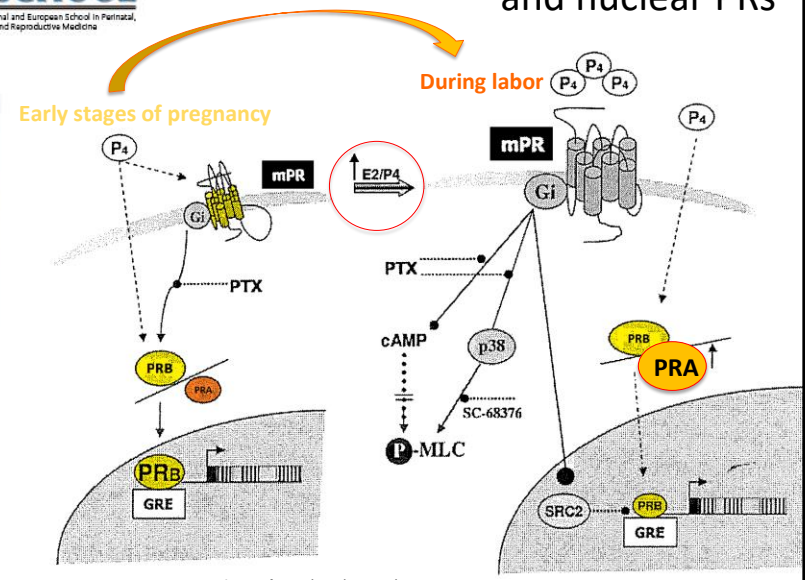
The combined actions of inhibitory transcription factors ZEB1 and ZEB2 (zinc finger E-box binding homeobox proteins 1 and 2) and members of the microRNA (miRNA)-200 family mediate the effect of progesterone on key contraction-associated proteins (CXN43 and OXTR) in the uterus during pregnancy.

The action of progesterone diminishes at the time of labor, and the steady state of the feedback loop drifts toward low ZEB levels and high miRNA-200 levels. ZEB1 and ZEB2 no longer inhibit *CNX43* and *OXTR*, which increases myometrial contractility…

and stimulates the onset of labor.

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

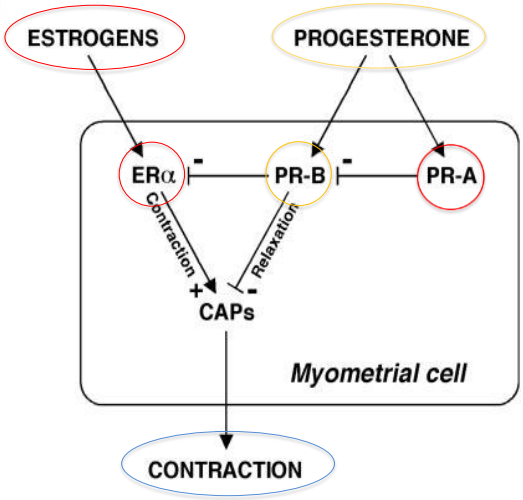
CROSS-TALK between membrane and nuclear PRs



Karteris et al. *Mol Endocrinol 2006;* **20***: 1519-1534*
Wang R et al. *Reprod Fertil Dev. 2014;* **30.** *doi: 10.1071/RD13430.*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Theoretical model for the role of the myometrial ER and PR systems in the regulation of human pregnancy and parturition

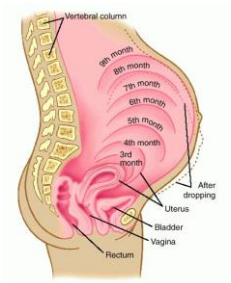


Mesiano et al. *J Clin Endocrinol Metab 2002;* **87***: 2924-2930*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Other effects of progesterone

Effect on uterine contractility



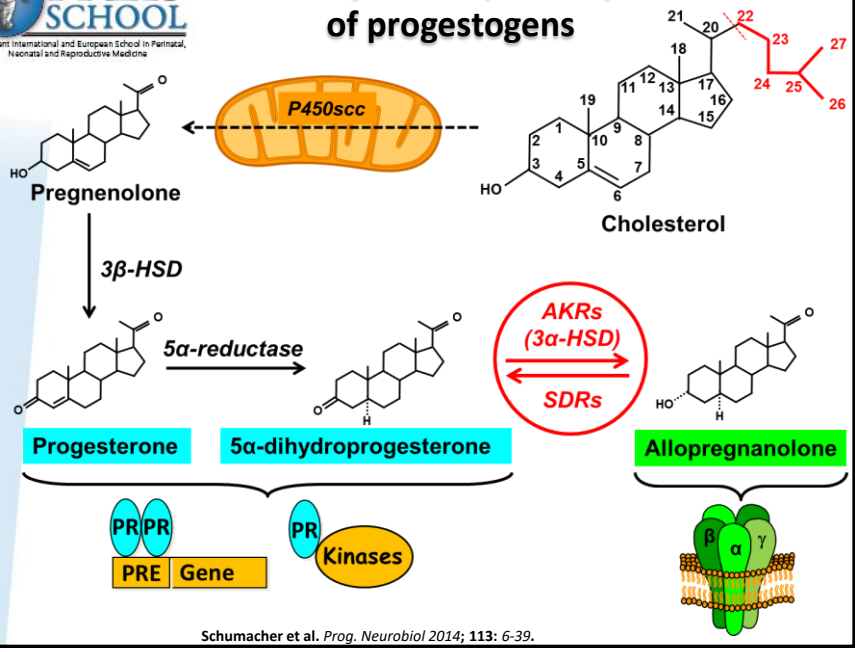
Neuroprotection of fetal brain

- Allopregnanolone is a neuroactive steroid
- Modulates GABAergic inbibition
- Control & balance fetal behaviour
- Protection of fetal brain from
  - hypoxia
  - ischemia

Hirst J et al J Ster Biochem 2014

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

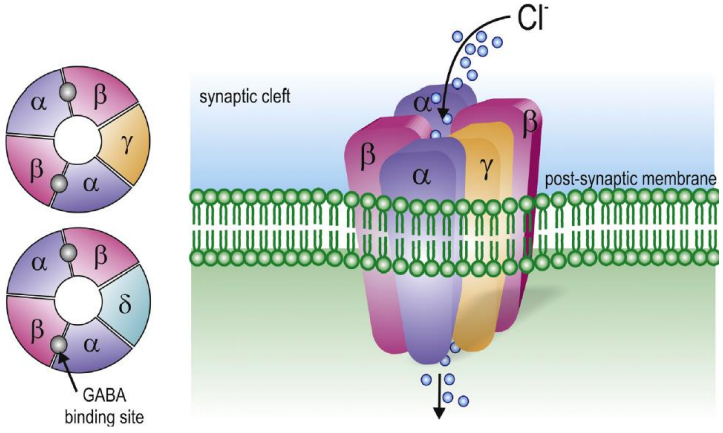
Biosynthetic pathway of progestogens



Schumacher et al. *Prog. Neurobiol 2014*; **113**: *6-39*.

PREIS SCHOOL
Permanent International and Neonatal and Rep

Neurosteroids and $GABA_A$ receptor

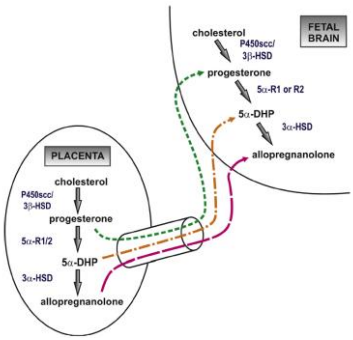


Allopregnanolone binds to a site in the transmembrane regions of the α and β subunits that is distinct from the GABA site, and acts to prolong opening time of the channel

Brunton et al. *Progress in Neurobiology 2014;* ***113****: 106-136*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Contribution of enzyme pathways in the sheep placenta and foetal brain to allopregnanolone concentrations.

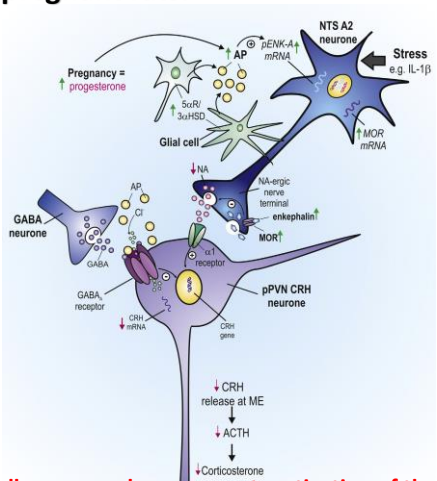


- Human studies suggest that the placenta contributes directly and indirectly to the allopregnanolone found in the circulation and potentially the foetal brain.
- The capacity of the maternal brain to generate neurosteroids is increased in pregnancy
- Allopregnanolone can modulate neuroendocrine responses to stress

Brunton et al. *Progress in Neurobiology 2014;* ***113****: 106-136*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Allopregnanolone-opioid mechanisms involved in suppressed HPA axis responses in late pregnant rats.



In pregnancy, allopregnanolone prevents activation of the CRH neurones, thereby inhibiting CRH release at the median eminence (ME) and preventing HPA axis responses to IL-1β.

Brunton et al. *Progress in Neurobiology 2014;* ***113****: 106-136*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Opptimum Trial

Primary outcomes

	Placebo group	Progesterone group	Unadjusted odds ratio (95% CI) or difference in means (95% CI)	p value (unadjusted)	Adjusted odds ratio (95% CI)* or difference in means (95% CI)	p value (adjusted*)
Fetal death or delivery <34 weeks of gestation	108/597 (18%)	96/600 (16%)	0·86 (0·64 to 1·17)	0·34	0·86 (0·61 to 1·22)	0·67
Neonatal morbidity or death	60/587 (10%)	39/589 (7%)	0·62 (0·41 to 0·94)	0·02	0·62 (0·38 to 1·03)	0·072
Cognitive composite score at 2 years†‡	97·7 (17·5)	97·3 (17·9)	−0·48 (−2·77 to 1·81)§	0·68	−0·48 (−2·77 to 1·81)§	0·68
Components of the obstetric outcome						
Fetal death	7/597 (1%)	8/600 (1%)	1·14 (0·41 to 3·17)	0·8	..	..
Liveborn delivery before 34 weeks	101/590 (17%)	88/592 (15%)	0·85 (0·62 to 1·15)	0·29	..	..
Components of the neonatal outcome						
Neonatal death	6/597 (1%)	1/600 (<1%)	0·17 (0·06 to 0·49)	0·0009¶	..	..
Bronchopulmonary dysplasia‖	18/574 (3%)	17/580 (3%)	0·94 (0·49 to 1·78)	0·84	..	..
Brain injury on ultrasound scan**	34/574 (6%)	18/584 (3%)	0·50 (0·31 to 0·84)	0·008	..	..

*

* p unadjusted = 0.02 (statistically significant)
¶ p unadjusted for previous pregnancy of at least 14 weeks because of small sample size.

Neonatal morbidity or death:

- **0.2% neonatal death** in progesterone group **1%** deaths in placebo group (***P=0.0009***)
- **3%** with brain injury in progesterone group and **6%** in placebo (***P=0.008***)

Norman et al. *Lancet 2016. Published **Online February 23**, 2016*
http://dx.doi.org/10.1016/ S0140-6736(16)00350-0

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Long-term effects of prenatal progesterone exposure on neurophysiological development and hospital admissions in twins up to 8 years of age (**PREDICT study**)

Ages Stages Questionnaire (ASQ) scores

N=437 children (progesterone, n=225; placebo, n=212).

Mean Total ASQ score higher in the progesterone vs placebo

269,0 vs 261,7 ***P=0.03***

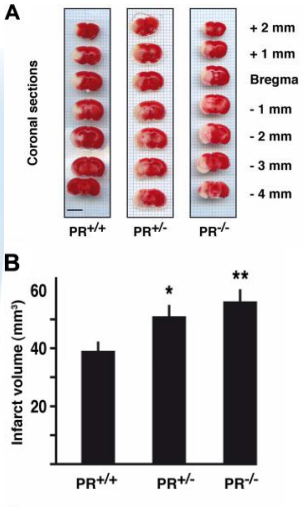
In dichorionic twins

- Risk of having a low ASQ score (<10th centile) decreased in the progesterone group: **OR 0.34 (0.14;0.86)**
- Overall higher total mean score **(p=0.01),** higher mean score in communication **(p=0.04),** gross motor skills **(p=0.02)** and personal/social **(p=0.04).**

Vedel C et al. Ultrasound Obstet Gynecol 2016; 48: 382–389

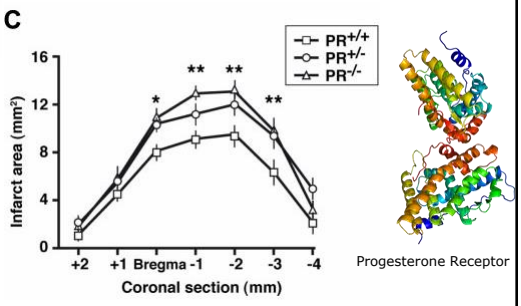
PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Progesterone Receptors (PR): A Key for Neuroprotection in Experimental Stroke



Influence of PR disruption on infarct volumes and areas at 24 h after middle cerebral artery (MCA) occlusion

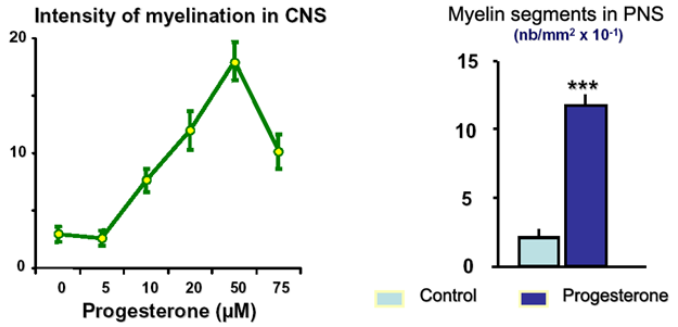
A: successive 1-mm-thick coronal brain sections (viable tissue red, infarcted tissue pale)
B: quantitative analysis of total infarct volumes
C: areas of damaged brain tissue



Liu A et al. *Endocrinology 2012;***153***:3747-57*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Neuroprotective effects of progesterone



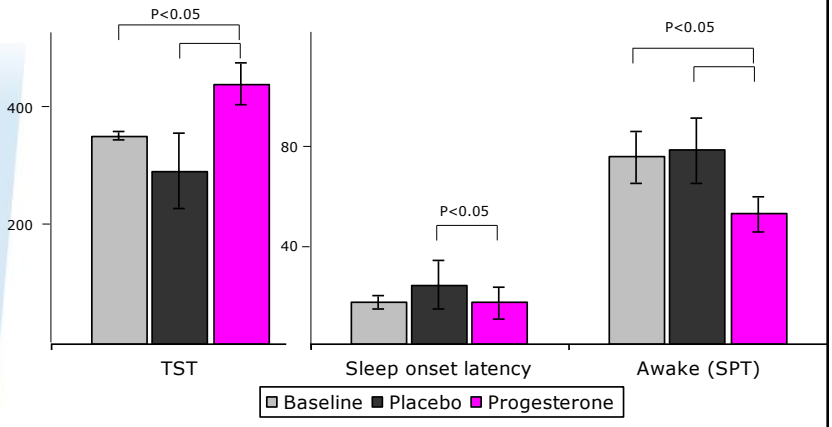
Progesterone accelerates myelination in organotypic cultures of rat CNS

Progesterone promotes the remyelination of axons after cryolesion of the mouse sciatic nerve

Schumacher *2003*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Oral Mic P4 and sleep EEG parameters * (mean +/- SD)



* before treatment (Baseline), at day 21 Placebo or Progesterone (300mg/d) treatment (*Utrogest caps*)
TST = Total Sleep Time
SPT = Sleep Period Time

Schüssler P et al. *Psychoneuroendocrinology 2008;* ***33****: 1124-1131*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Oral Mic P4 prevents sleep disturbances


Progesterone Prevents Sleep Disturbances and Modulates GH, TSH, and Melatonin Secretion in Postmenopausal Women

- Progesterone (P4) had no effect on undisturbed sleep
- P4 restored normal sleep when sleep was disturbed (P4 increases deep sleep while currently available hypnotics tend to inhibit deep sleep), acting
- P4 acts as a "physiologic" regulator rather than as a hypnotic drug.
- Use of progesterone might provide novel therapeutic strategies for the treatment of sleep disturbances, in particular in aging where sleep is fragmented and of lower quality.

Caufriez et al. *J Clin Endocrin Metab 2011 2011,* **96,** *E614-E623. doi:10.1210/jc.2010-2558*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Progesterone and influence of the route of administration

Mechanism of action

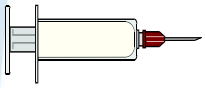
PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Routes of administration

ORAL

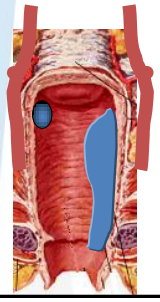
→ 90% metabolized after 1st hepatic passage
→ High inter-individual variability
→ rapid increase in plasma concentration followed by gradual decrease
→ **metabolites 5-α & 5-ß** possess hypnotic and anxiolytic effects (via GABA rec)

I.M.



Discomfort and painful injection
→ Supraphysiological blood levels
→ At least twice weekly requiring nurse assistance
→ Granulomas (>oil), allergy and dry abscesses
→ Risk for acute eosinophylic pneumonia
→ Choice between daily and "depot"

VAG



VAG CAPS
Minimal or no *discomfort*
→ Constant systemic levels
→ Avoid hepatic passage, safest
→ 1st uterine passage

VAG GEL
Cloddy vaginal discharges
→ Perineal pains (reported ≥ 5% patients)
→ Painful or difficult intercourse, genital itching, genital yeast infection, urinary tract infection (reported in 1 to 5% of patients)

Plagiarized and adapted from ***GC Di Renzo***, personal communication

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Metabolization of oral Natural Progesterone

Oral–administered progesterone undergoes several successive metabolisation steps:

- ✓ in the gut (bacteria with 5b-reductase activity)
- ✓ in the intestinal wall (5a-reductase activity)
- ✓ in the liver (5b-reductase, 3a-and 20a-hydroxylase activities)

5a-pregnanolone and 5b-pregnanolone (GABA $_A$)
5a-pregnanedione and 5b-pregnanedione (anti-mitotic, tocolytic)

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Effect of progesterone and his metabolites on spontaneous uterine contractility of pregnant women at term

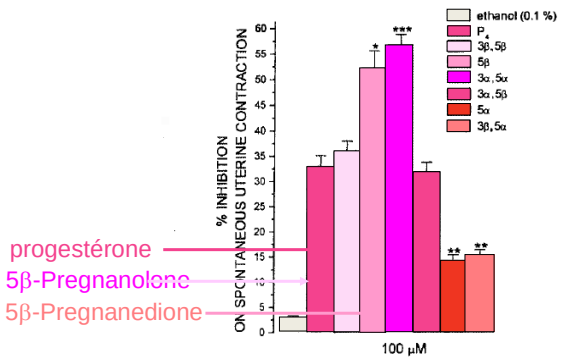


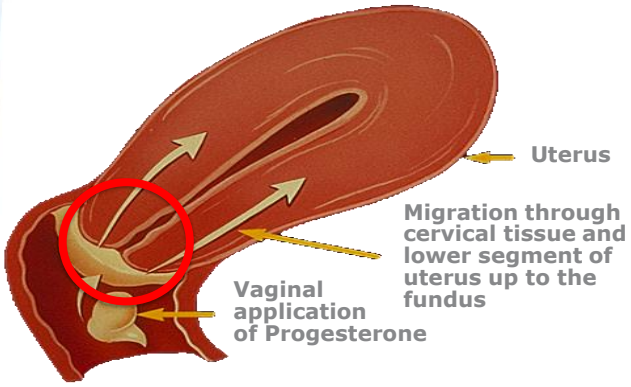
Fig. 3. Comparison of the relaxing effect induced by progestins at equimolar concentration (100 µM) on spontaneous uterine contractility of pregnant women at term. Each bar represents the mean ± SEM (n ≥ 6). * p<0.003, ** p<0.0005, *** p<0.0001 vs. progesterone (P_4). Note the effect of all progestins was significantly different (p<0.0001) vs. ethanol at 17.14 mM (0.1 %), a concentration identical to those use as solvent for progestins.

Perusquia et al. *Life Sciences 2001; **68**: 2933 - 2944*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Use of exogenous progesterone

Vaginal administration (route)



First uterine pass effect / targeted delivery

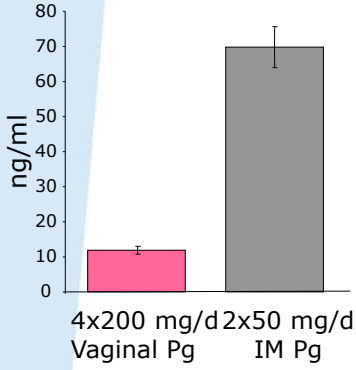
Cicinelli E et al, *Obstet Gynecol 2000;* **95***: 403-6*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

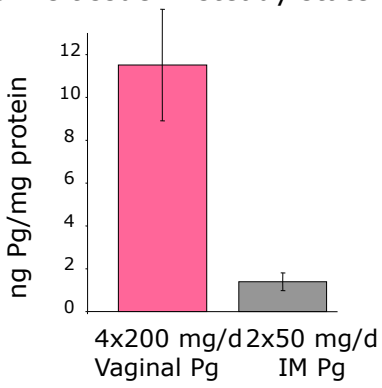
Use of exogenous progesterone

Pharmacokinetics data: **vaginal route vs IM**

Plasma progesterone concentrations in steady state



Progesterone concentrations in uterine tissue in steady state



Miles A et al, *Fertil Steril 1994;* **62**: *485-90*

Characteristics of Mic P4 versus synthetic Progestogens

Natural Micronized Progesterone (MP)

=

Exact chemical duplicate of Progesterone produced by the human body

≠

Synthetic analogues of Progesterone labeled *Progestogens* or *Progestins*

Major Differences in *Pharmacodynamics* of Micronized progesterone versus synthetic progestins

- Tranquilizing effect
- Anti-androgenic effect
- Diuretic effect

Synthetic progestins

- Synthetic analogues of Progesterone have been developed to make the hormone available orally
- First developed for use as contraceptive agent
- Many of these compounds bind to receptors for glucocorticoids, androgen and mineralocorticoids

→ side effects (acne, weight gain, depression, mood swings, irritability)

Natural Progesterone vs Synthetic progestins

Pregnanolone metabolites are physiological
anxiolytic and hypnotic steroids
Interacting with $GABA_A$ receptor in CNS

≠

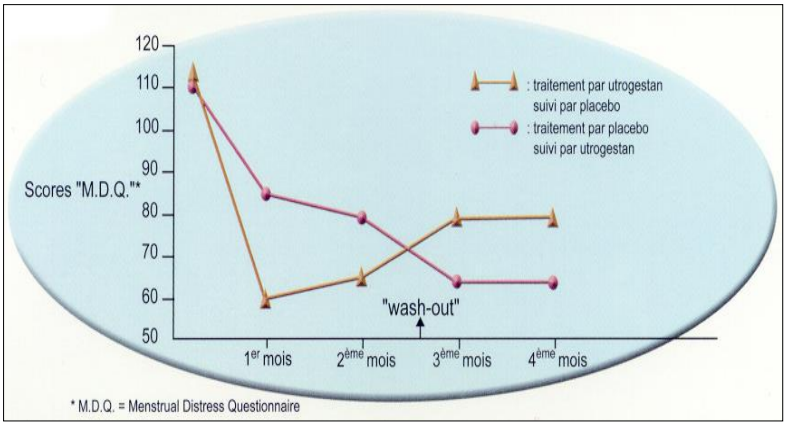
Synthetic progestins are not pro-drugs for these metabolites
Negative effect on mood

No anxiolytic, sedative, hypnotic effect

Bitran et al. *J Neuroendocrinol 1995;* ***7(3)****: 171-7*
Rapkin et al. *Obstet Gynecol 1997;* ***90(5)****: 709-14*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Oral Mic P4 and tranquilizing effect

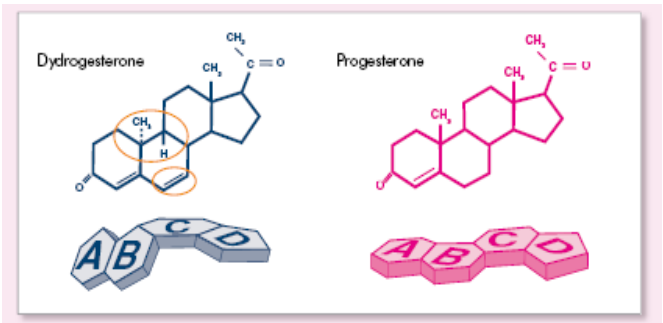


Efficacy of oral Mic P4 in Premenstrual Syndrome treatment

Dennerstein L et al. *Br Med J* 1985; **290**: 1617-1621

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Dydrogesterone versus Progesterone



Dydrogesterone is a retroprogesterone, a stereoisomer of progesterone:

1. **H** $_{30}$ instead of **H** $_{28}$ in progesterone: $C_{21}H_{30}O_2$ vs $C_{21}H_{28}O_2$
2. No Double bond in C 6-7
3. Progesterone is a **flat (and not truncated)** molecule
4. Progesterone does not bind same receptors

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Treatment of premenstrual Syndrome
A double-blind Trial of dydrogesterone

Summary

A double-blind randomised crossover trial of oral micronised progesterone and placebo had demonstrated that progesterone had beneficial effects over placebo for some mood and physical premenstrual symptoms. A further trial using identical methodology was carried out to assess whether dydrogesterone would have the same beneficial effects. Prospective assessment confirmed the presence of a premenstrual syndrome in 30 women. Of these, six withdrew during the 4 months of the study. Twenty-four women completed the double-blind crossover protocol. All women were interviewed premenstrually before treatment and in each month of treatment. They completed the Moos Menstrual Distress Questionnaire, Beck Depression Inventory, Spielberger State Anxiety Inventory, Mood Adjective Checklist and a Daily Symptom Record. Analysis of data found an overall beneficial effect of being treated for most variables. Further analysis showed that the most major effects occurred in the first 2 treatment months. This study could find no evidence that dydrogesterone was more effective than placebo in treating premenstrual complaints.

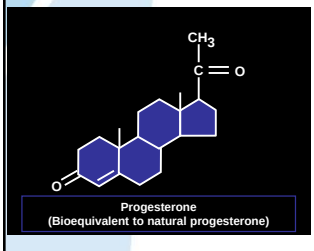
This study could find no evidence that dydrogestreone was more effective than placebo in treating premenstrual complaints

Dennerstein et al. *Journal of Affective Disorders* 1986; **11**: 199-205

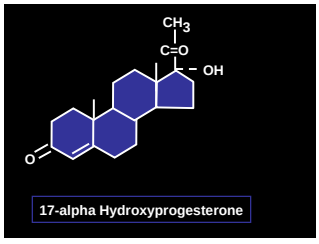
PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Progestogen

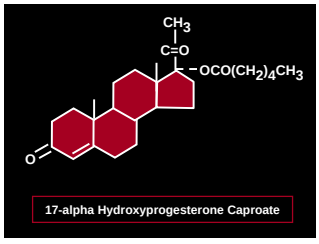
Three Different Compounds



Progesterone
(Bioequivalent to natural progesterone)



17-alpha Hydroxyprogesterone



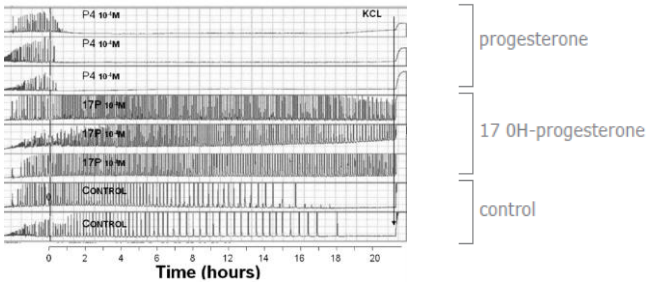
17-alpha Hydroxyprogesterone Caproate

P4 **17-OHP** **17-OHP-C**

Natural compounds **Synthetic**

Tocolytic effect of progesterone versus synthetic progestins

Changes in contractility in progesterone and 17 OH-progesterone treated myometrial strips [2]



- Progesterone reduces myometrial oxytocin-induced contraction [1]
- Progesterone, but not 17 OH-progesterone, directly inhibits uterine contractility [2,3]
- 17P did not delay the interval to delivery in women with tocolysis-arrested preterm labor [4,5]

1. Chanrachakul B et al. *Am J Obstet Gynecol 2005;* **192***: 458-63.* **2. Ruddock NK et al.** *Am J Obstet Gynecol 2008;* **199***: 391-7* . **3. O'Brien JM et al.** *Am J Perinatol 2010*; **27***: 157-62.* **4. Briery C et al**. *J Mat Fet Neonat Med 2014.* doi: 10.3109/14767058.2014.892922 . **5. Rozenberg P et al**. *Am J Obstet Gynecol 2012;* **206***. e1-9.*

Progesterone is given prophylactically to prevent preterm birth among women

- Meis et al, 2003. *N Engl J Med*
- Da Fonseca et al, 2003. *Am J Obstet Gynecol*
- Fonseca et al, 2007. *N Engl J Med*
- O'brien et al, 2007. *Ultrasound Obstet Gynecol*
- DeFranco et al, 2007. *Ultrasound Obstet Gynecol*
- Rai et al, 2009. *Int J Gynecol Obstet*
- Mahji et al, 2009. *J Obstet Gynecol*
- Cetingoz et al, 2009. *Arch Gynecol Obstet*
- Hassan et al, 2011. *Ultrasound Obstet Gynecol*
- Rode et al, 2011. *Ultrasound Obstet Gynecol*
- Maher MA et al, 2013. *Acta Obstet Gynecol Scand*
- Norman J et al*, 2016. The Lancet*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Challenges in preterm delivery prevention and management

Strategy in the prevention

Identification of risk factors

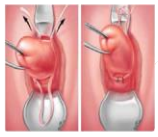
Prior history of preterm birth

Twin pregnancy

Short cervix at scan

TVS-cervical length is the single most powerful predictor for PTD in the index pregnancy.

Progesterone | **Cerclage** | **Pessary**

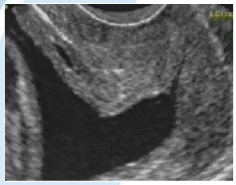

On the courtesy of Eduardo Fonseca

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Challenges in preterm delivery prevention and management

Strategy in the prevention

Short cervix



<25 mm

No prior PTD

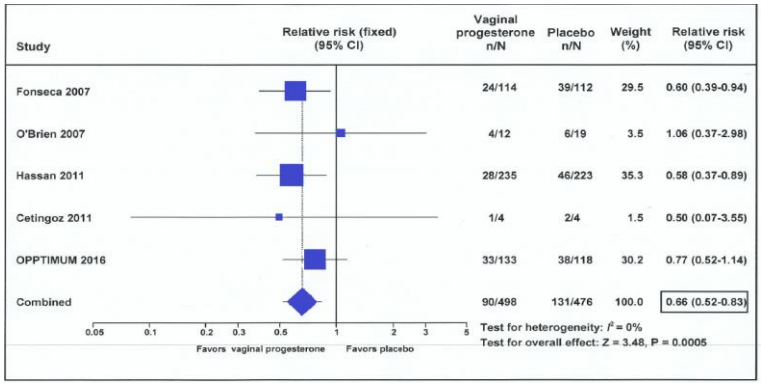
Twins plus Short CxL

Prior PTD Plus Short CxL

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Effect of vaginal progesterone

on preterm birth ≤ 34 weeks of gestation



CONCLUSION: Vaginal progesterone administration to asymptomatic women with singleton gestation and a sonographic short cervix decreases preterm birth ≤ 34 weeks of gestation, neonatal morbidity and mortality.

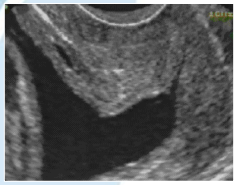
Romero R et al. *Ultrasound Obstet Gynecol 2016;* **48(3)***: 308-17*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Challenges in preterm delivery prevention and management

Strategy in the prevention

Short cervix



<25 mm

No prior PTD

Twins plus Short CxL

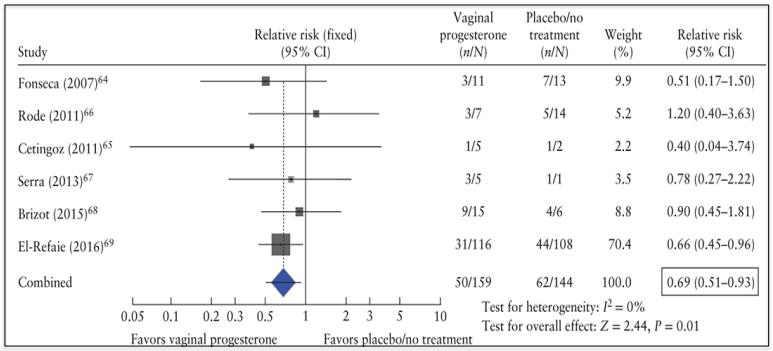
Prior PTD Plus Short CxL

On the courtesy of Eduardo Fonseca

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Effect of vaginal progesterone

on preterm birth in twin gestation



CONCLUSION: Administration of vaginal P4 to asymptomatic women with a twin gestation and a sonographic short cervix in the mid-trimester reduces the risk of preterm birth occurring at < 30 to < 35 gestational weeks, neonatal mortality and some measures of neonatal morbidity, without any demonstrable deleterious effects on childhood neurodevelopment.

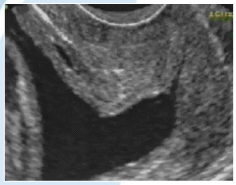
Romero R et al. *Ultrasound Obstet Gynecol 2017;* **49(3)***: 303-14*

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Challenges in preterm delivery prevention and management

Strategy in the prevention

Short cervix



<25 mm

- **No prior PTD**
- **Twins plus Short CxL**
- **Prior PTD Plus Short CxL**

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

Prevention of PTD in singletons

Prior PTB and short cervix

Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis

	Cerclage	Progesterone
Del <35 wks	↓ 33%	↓ 41%
Composite morbidity	↓ 40%	↓ 70%
Perinatal mortality	↓ 35%	↓ 27%

The selection of the optimal treatment may depend upon adverse events, cost and patient/clinician preferences.

Conde-Agudelo, et al. *Am J Obstet Gynecol* 2013; **208**: 1-42.

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

CONCLUSION

- The **role of progesterone** in the **physiopathology of pregnant women** is **crucial** from conception until delivery.
- There is **strong biological plausibility** to support exogenous progesterone for the management of prevention of preterm birth in women at risk with a short cervix and/or a history of preterm delivery.
- The **optimal** dose, **route of administration** and **duration** remains to be determined in **symptomatic women** and in **pregnancy maintenance after tocolysis.**
- **Neonatal effects, health infant** and cost-effectiveness with vaginal micronized progesterone are now available with a level 1 of evidence.

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

FUTURE PERSPECTIVES

- Allopregnanolone has important roles during pregnancy in quelling the responsiveness of the body's major neuroendocrine stress response system, the HPA axis.
- Allopregnanolone restrains responses of neurons that make and secrete oxytocin to stimulate uterine contractions during birth; this action of allopregnanolone is considered to help prevent preterm births.
- The actions of allopregnanolone on oxytocin neurons are partly direct, on $GABA_A$ receptors, and partly indirect through induction of an opioid peptide inhibitory mechanism in the brainstem, in the noradrenergic pathway that conveys neural signals from the uterus.
- The foetal brain is also exposed to, and produces allopregnanolone, reducing the impact of hypoxia, which may be experienced during a difficult birth, and result in excitotoxic brain damage.
- Preterm birth has similar consequences, and the reduced allopregnanolone production in the brain continues after birth, with impaired myelination and neuro behavioral outcomes.

Brunton et al. *Progress in Neurobiology 2014;* ***113****: 106-136*