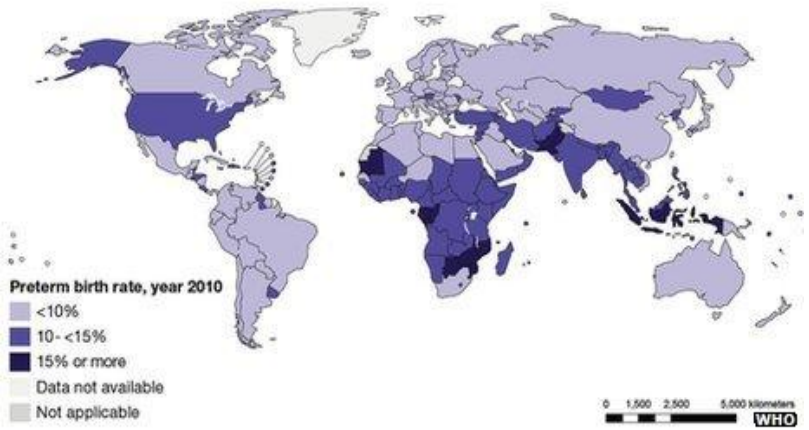
Additional treatment with natural progesterone prolongs gestation in women with preterm labour

Vladic Stjernholm Ylva, Vladic Tomislav, Marchini Giovanna
Derpartment of Women s and Children s Health
Karolinska University Hospital
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Stockholm, Sweden

Preterm birth

Preterm birth (PTB) occurs in 5% in developed and up to 18% in developing countries.

The cause of 70% of all perinatal morbidity and mortality.



www.who.int

Tocolysis

Oxytocin receptor antagonist (atosiban)

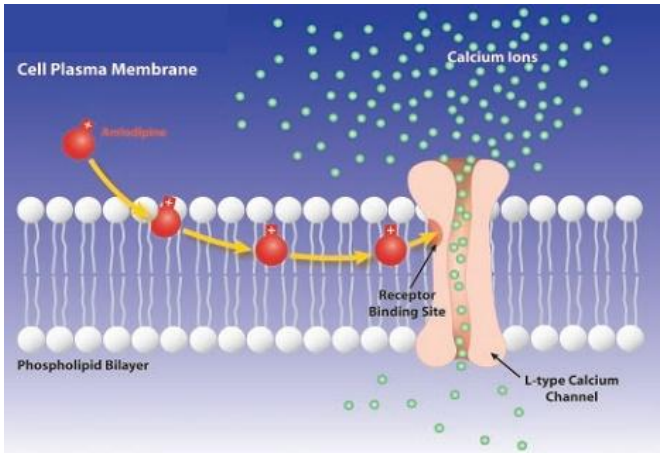
β_2-receptor agonist (terbutaline)

Ca^{2+}channel blocker

Magnesium sulfate

Prostaglandin syntethase inhibitor (NSAID)

Nitric oxide donors



Do not prevent PTB

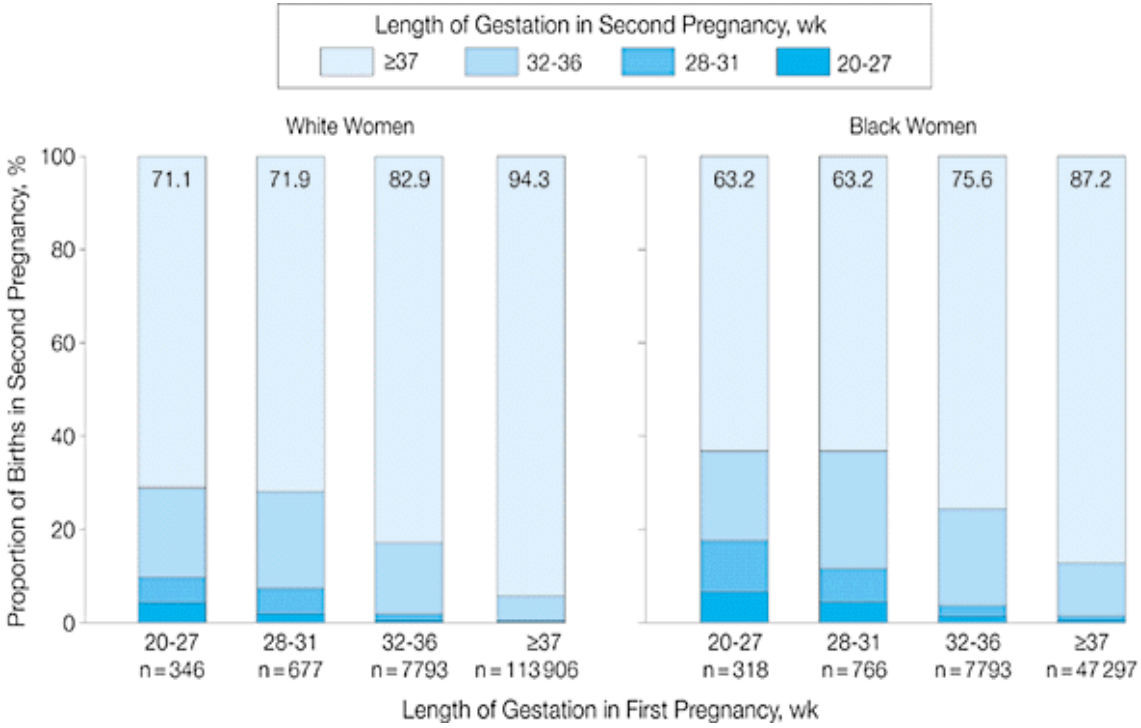
Haas DM, et al. BMJ 2013;345:e6226

Increasing cervical competence

Author	Study group	Inclusion	Progesterone	Results
Meis P, *et al.* NEJM 2003	Previous PTB n=463	18 wk	17OHPC 250 mg/wk	PTB < 32 wk 11,4 vs 19,6% (RR 0.58)
da Fonseca EB, *et al*. AJOG 2003	Previous PTB n=142	25-26 wk	P 100 mg/d	PTB < 34 wk 2,8% vs 18,6% (p < 0,05)
O Brien JM, *et al*. UOG 2007	Previous PTB n=659	18-23 wk	P 90 mg/d	PTB < 35 wk 22,7% vs 26,5% (NS)
da Fonseca EB, *et al*. NEJM 2007	Asymptomatic CL ≤ 15 mm n=250	20-24 wk	P 200 mg/d	PTB < 34 wk 19,2, % vs 34,4% (p=0,03)
Hassan S, *et al*. OG 2011	Asymptomatic CL 10-20 mm n=458	19-23+6 wk until 36+6 wk	P 90 mg/d	PTB < 35 wk 14,5% vs 23,3% (p=0,02) PTB < 37 wk (NS)

Previous preterm birth

Only 10 (-20)%



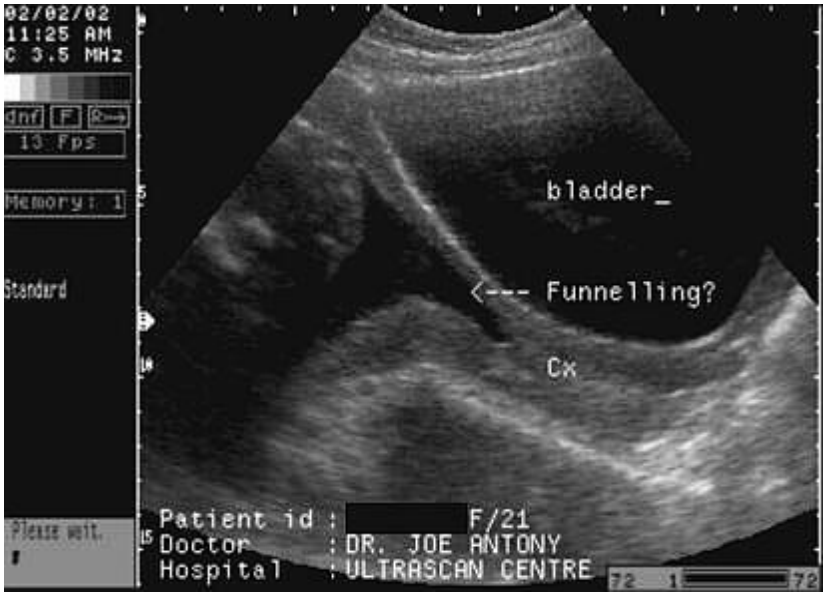
Adams M, et al. JAMA 2000;283:1591

Cervical length

Short CL ≤ 25 mm is the primary risk factor for PTB

Less than 2% has a CL ≤ 15 mm at midgestation -

risk 50% PTB before 33 wk



Iams JD, et al. AJOG 1998;178:1035

To MS, et al. Lancet 2004;363:1849

Hassan S, et al. AJOG 2000;182:1458

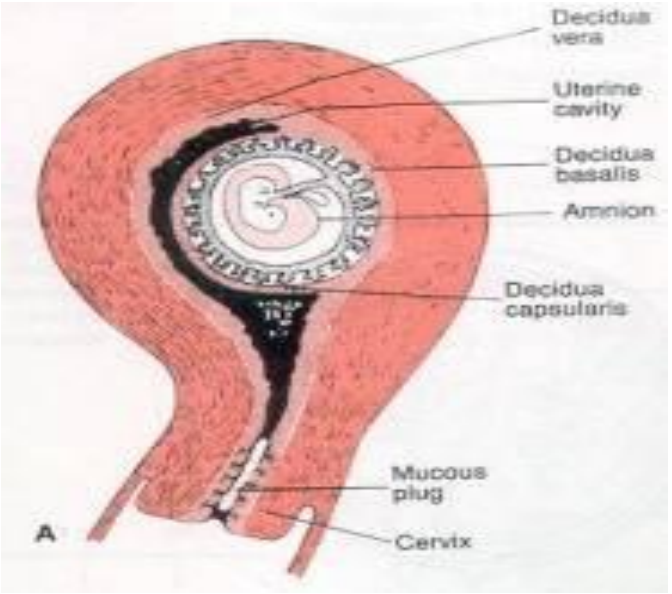
Progesterone effects

Uterine quiescence
- Oxytocin response ↓
- Prostaglandin synthesis ↓
- Gap junctions ↓

Cervical competence
- Metalloproteinases (MMPs)
- Inflammatory activity ↓

Non-genomic

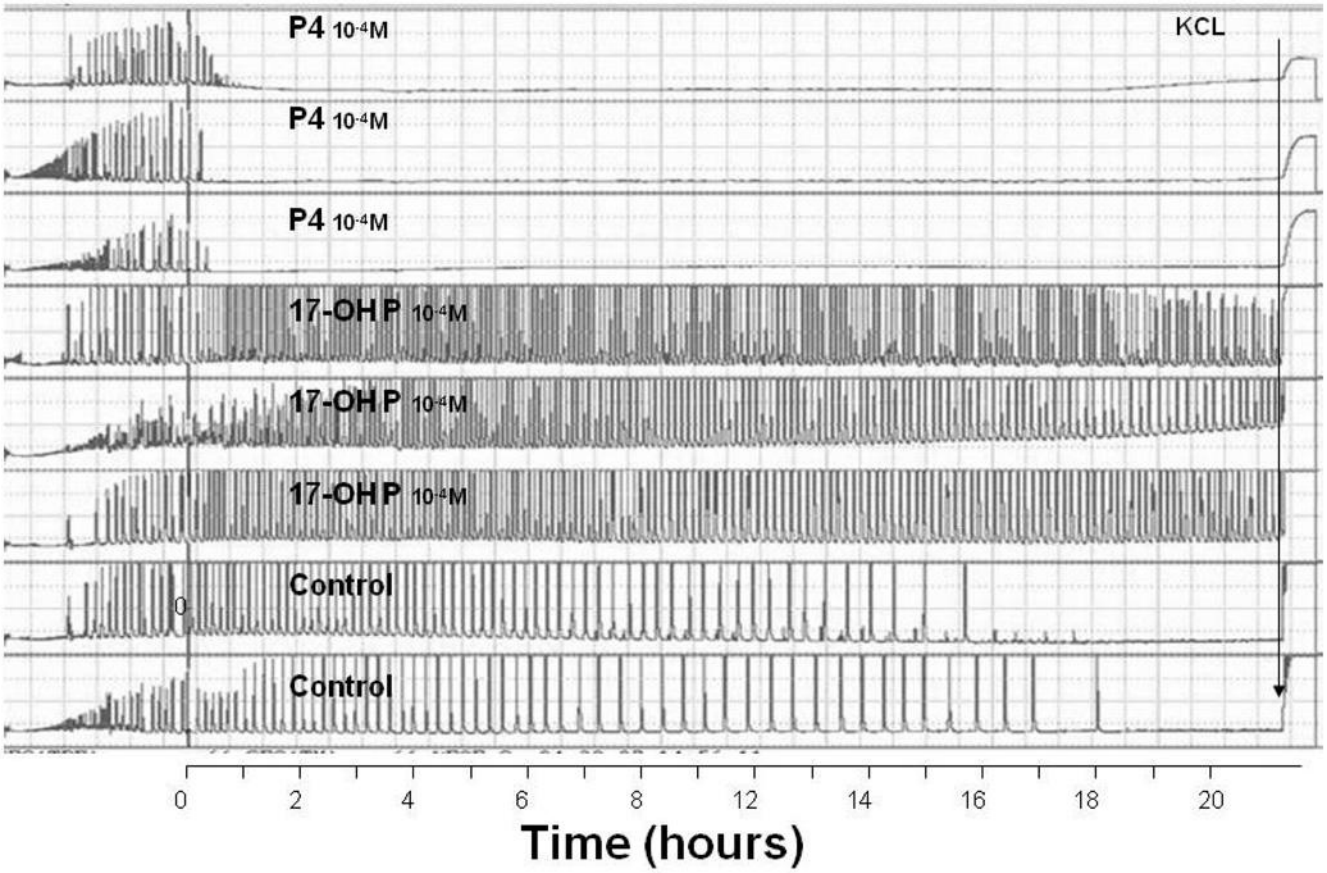
Genomic



Csapo AI. Am J Anat 1956;98:273
Garfield R, et al. Am J Cell Physiol 1980;238:81
Zakar T & Hertelendy F. AJOG 2007 doi:10
Lucovnik M, et al. AOGS 2011;90:105

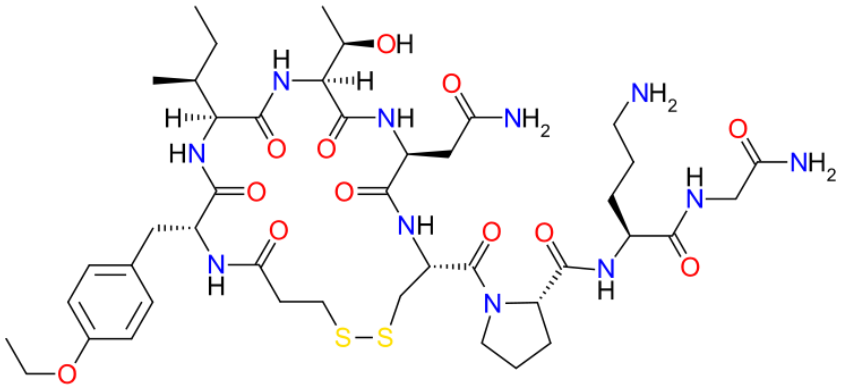
P but not 17OHPC suppresses myometrial contractions

Ruddock N, et al AJOG 2008;199:391



Hypothesis

P could prolong pregnancy after the onset of myometrial contractions.

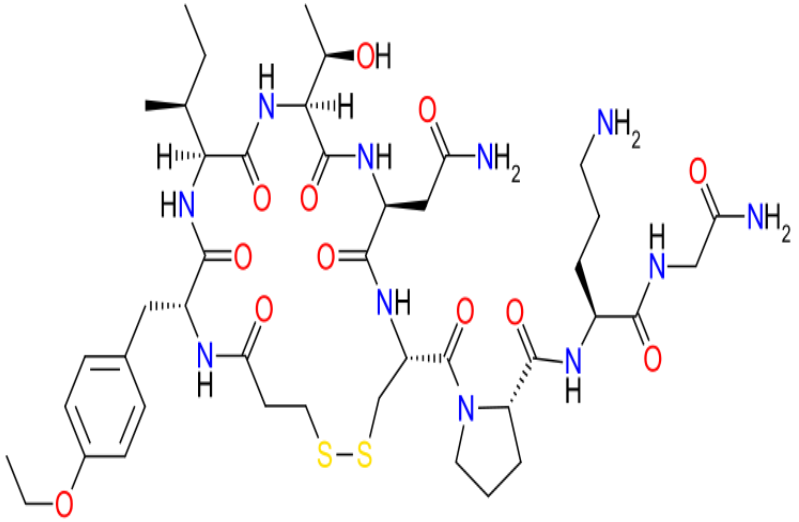


Kuon RJ, et al. AJOG 2010;202:455

Clinical data

Study group

P gel 90 mg/d 24-34 wk



Placebo group

Placebo gel 1/d

Control group

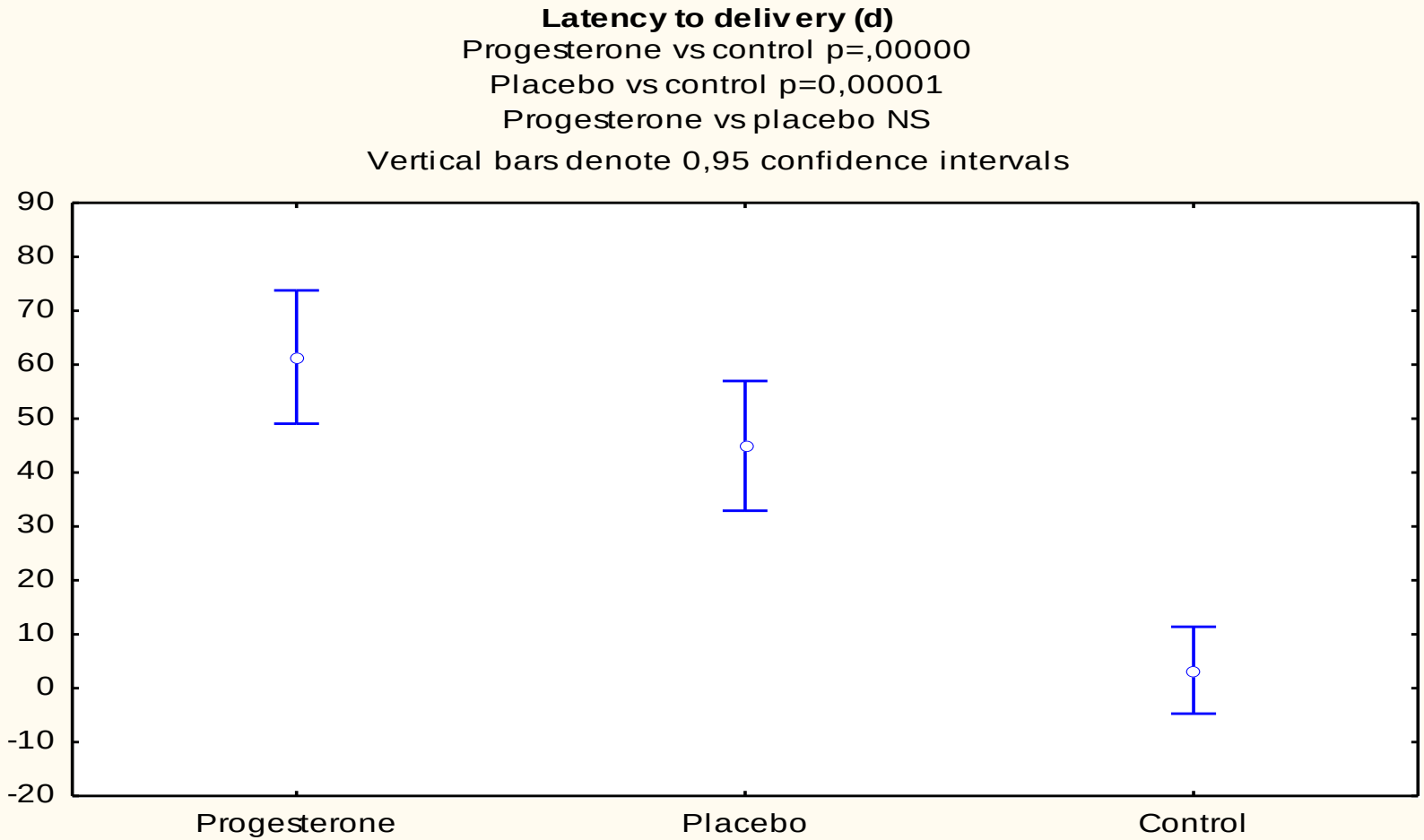
Tocolysis alone

Maternal outcomes

Progesterone vs control *p < 0.000001
Progesterone vs placebo NS

	Progesterone n=17	Placebo n=18	Control n=40
Latency to delivery (d)	62*	45	3*
CL at inclusion	9.8 (1-22)	9.7 (1-22)	Dil < 3 cm
C-reactive protein	7	5	10
PTB before 37+0 wk n (%)	5 (29) *	9 (50)	40 (100) *
PTB before 34+0 wk n (%)	9 (53) *	10 (56)	40 (100) *
Adverse maternal effects	0	0	0

Latency to delivery



Neonatal outcomes

Progesterone vs control *p < 0.0001, ** p < 0.00001
Progesterone vs placebo NS

Characteristic	Progesterone n=17	Placebo n=18	Control n=40
Birth weight < 1500 g n (%)	4 (24) *	7 (39)	31 (78)*
Birth weight < 2500 g n (%)	7 (41) **	11 (61)	39 (98)**
Apgar score less than 7 at 5	1 (6) *	2 (11)	15 (38)*
Intrauterine death	0	0	0

Comment

	Study group	Inclusion	Treatment	Results
Borna S & Sahabi N. ANZJOG 2008;48:58	n=70 24-34 wk	Tocolysis Mg-SO_4 48 hours Cervical dilatation ≤ 2 cm	P vag suppositories 400 mg/d vs No treatment	Latency delivery 36 vs 24 d p=0.03 PTB < 37 wk? Recurrent PTL NS
Sharami SH, et al. Royan Inst J Fertil Steril 2010;4:45	n=87 n=87 28-36 wk	Pethidine Tocolysis Mg-SO_4 48 hours Cervical dilatation ≤ 2 cm	P vag suppositories 200 mg/d vs Placebo	Latency delivery 24 vs 17 d P=0.004 PTB < 34 wk NS PTB < 37 wk NS

Secondary objectives

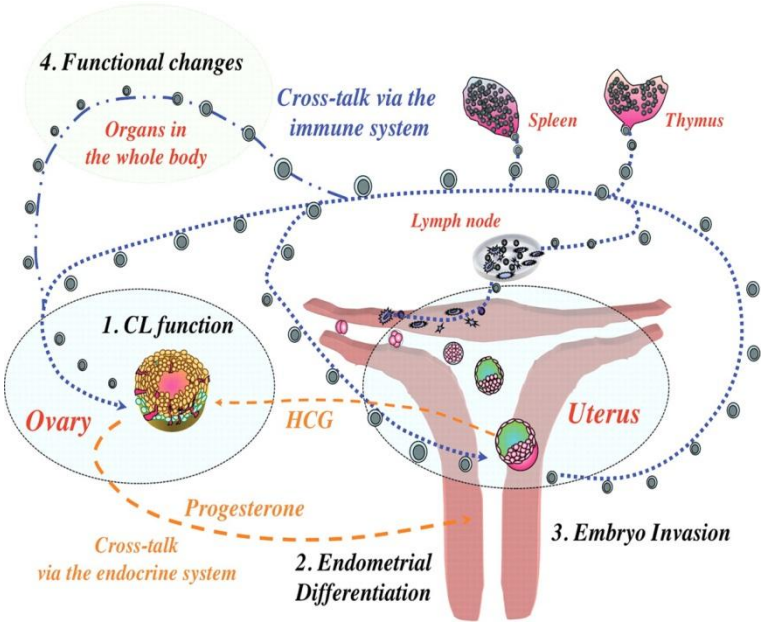
Reduction of stress and anxiety

Immunomodulation

Stites DP, Siiteri PK Immunol Rev 75:117-138.

Bauleiu EE, Schumacher M. Steroids 2000:65

Hellgren C, etal. Low allopregnanolone is associated with symptoms of depression in late pregnancy. Neurophysiol 2014;69



Fujivara H, et al. Mol Hum Reprod 2009;15

Stress

Maternell stress in 25%

Fetal stress

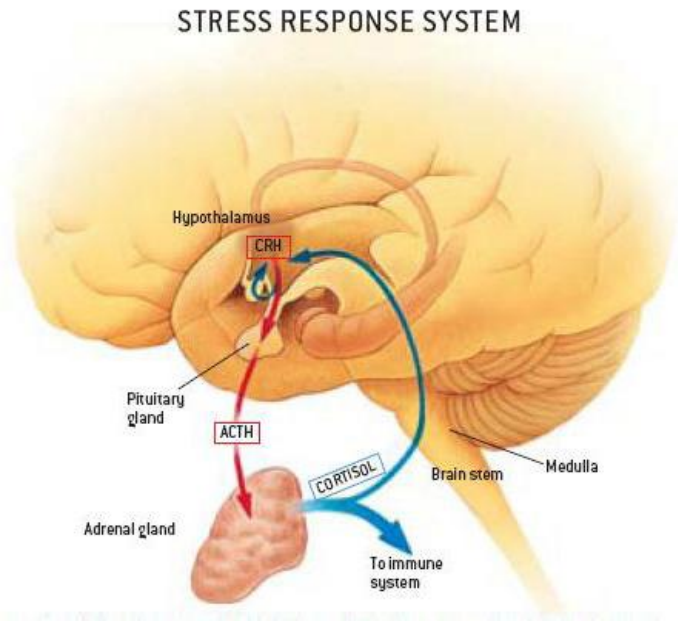
CRH

↓

DHEAS cortisol

↓ ↓

estradiol, estriol ↑ progesterone ↓

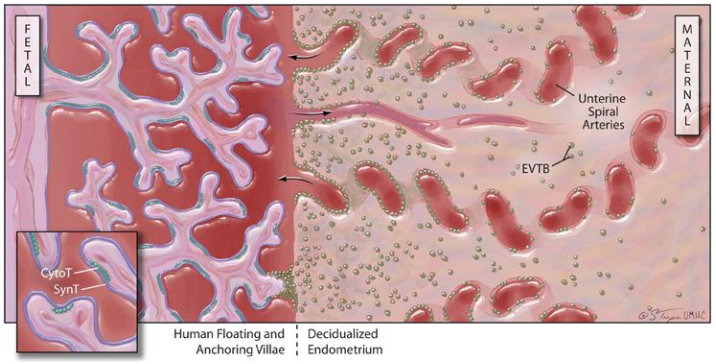


Maclean M, et al. Nature Med 1995;1:460

Loomans E, et al. Eur J Public Health 2012;1.

Immunomodulation

Progesterone induced blocking factor (PIBF) by acting on the phospholipase A2 enzyme interferes with arachidonic acid metabolism, induces a Th2 immune response, and by controlling NK activity exerts an anti-abortive effect.



Szekeres Bartho J, et al. J Int Immunopharm 2001;1:1037

Conclusion

Treatment with P increased the latency to delivery in women with preterm labor as compared to intravenous tocolysis alone

($p < 0.000001$).

A treatment with a placebo gel containing the vehicle increased latency in a manner comparable to P.

