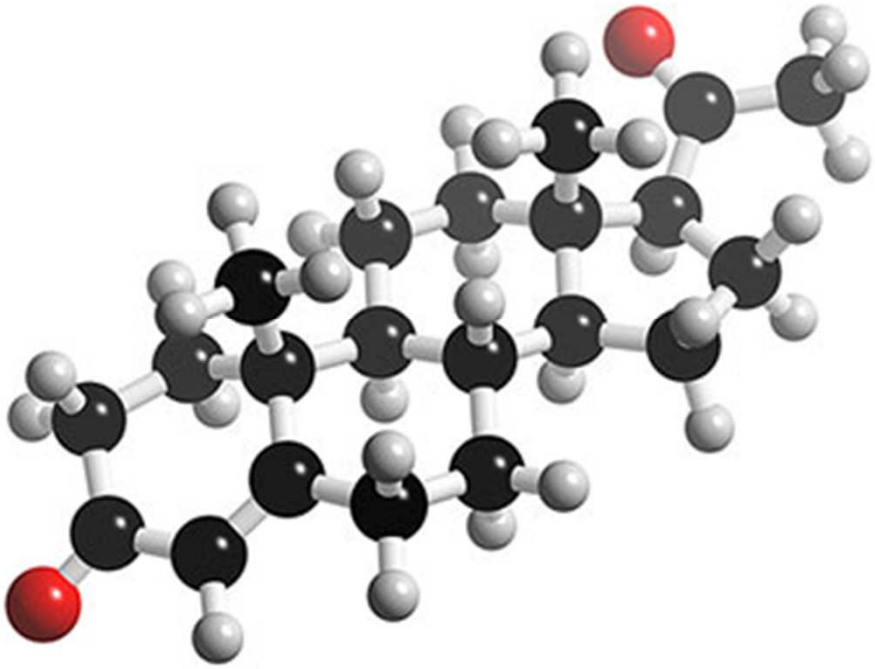
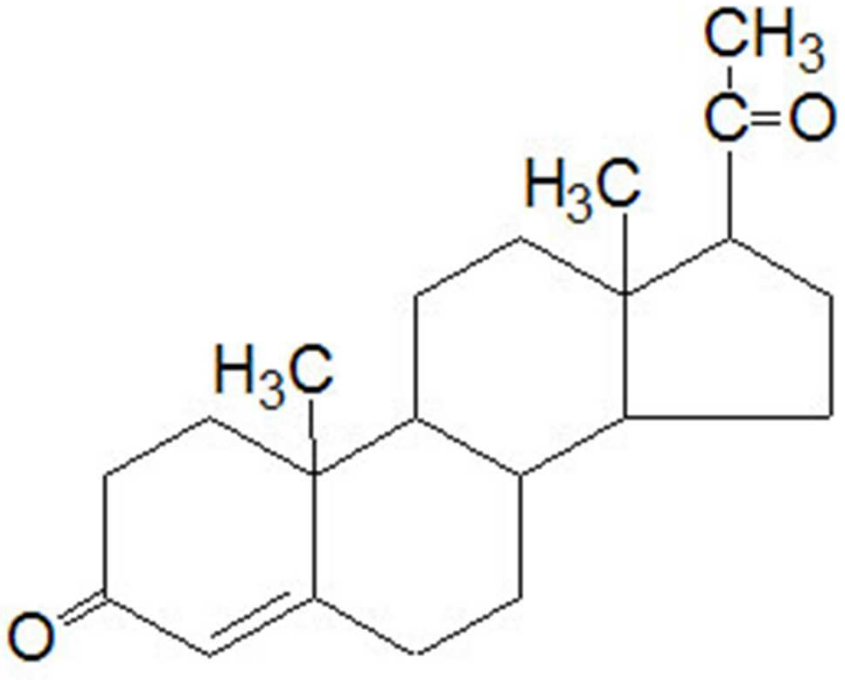
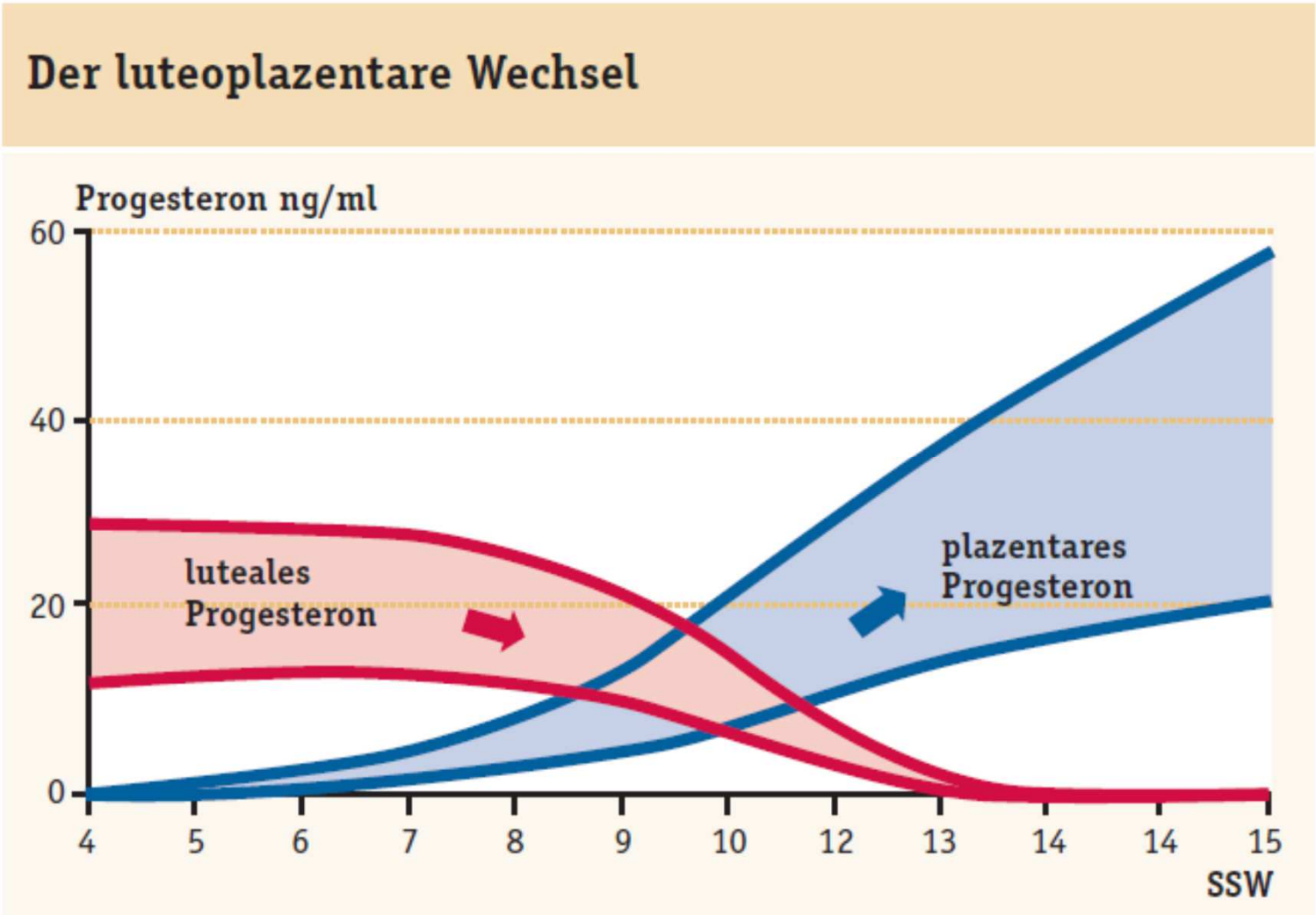
Progesteron zur Frühgeburtsprophylaxe?



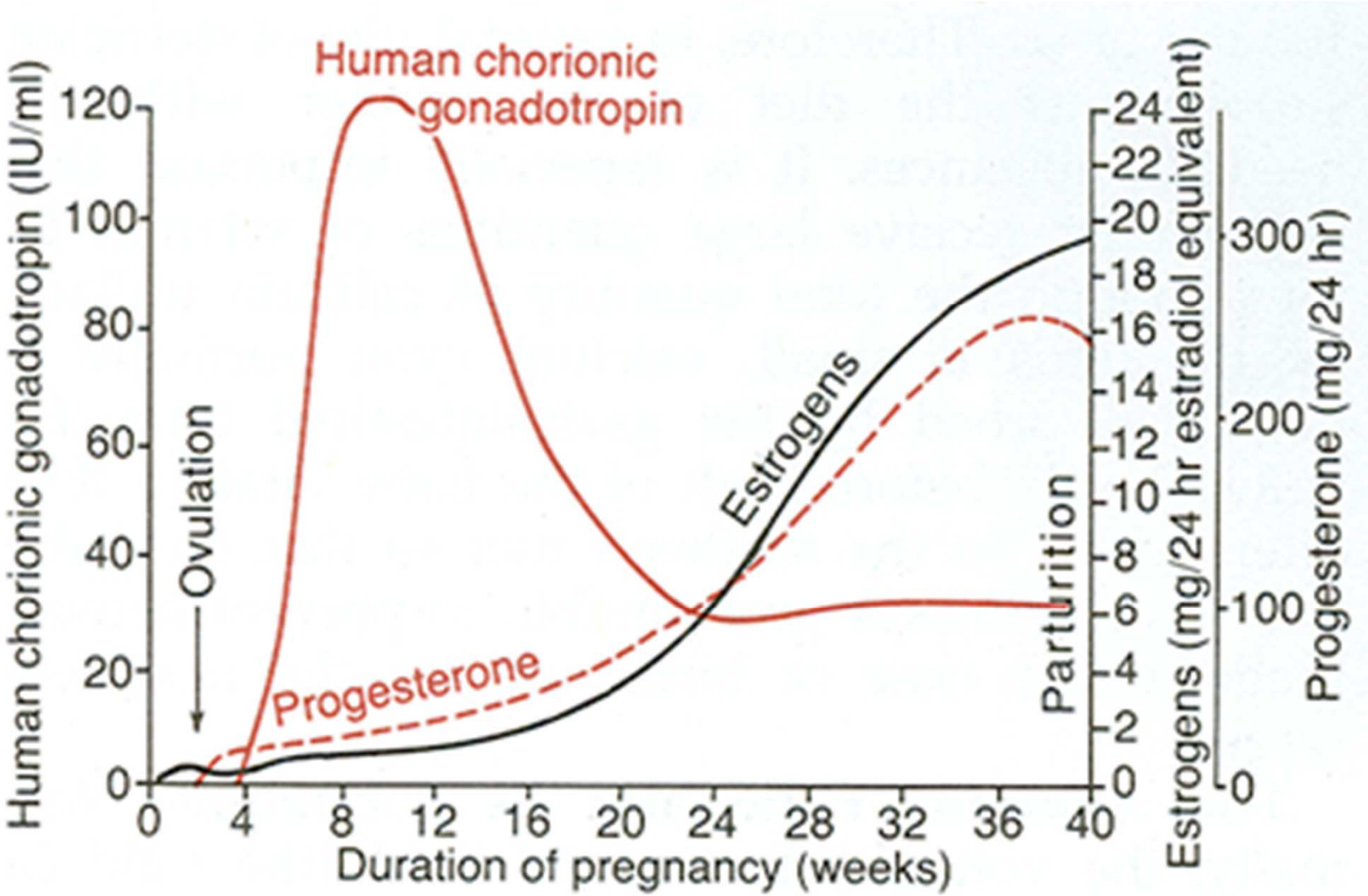


F. Moser, UFK Graz, Juni 2013

Verlauf der Progesteronspiegel im ersten Trimenon der normalen Schwangerschaft



Hormonspiegel im Schwangerschaftsverlauf



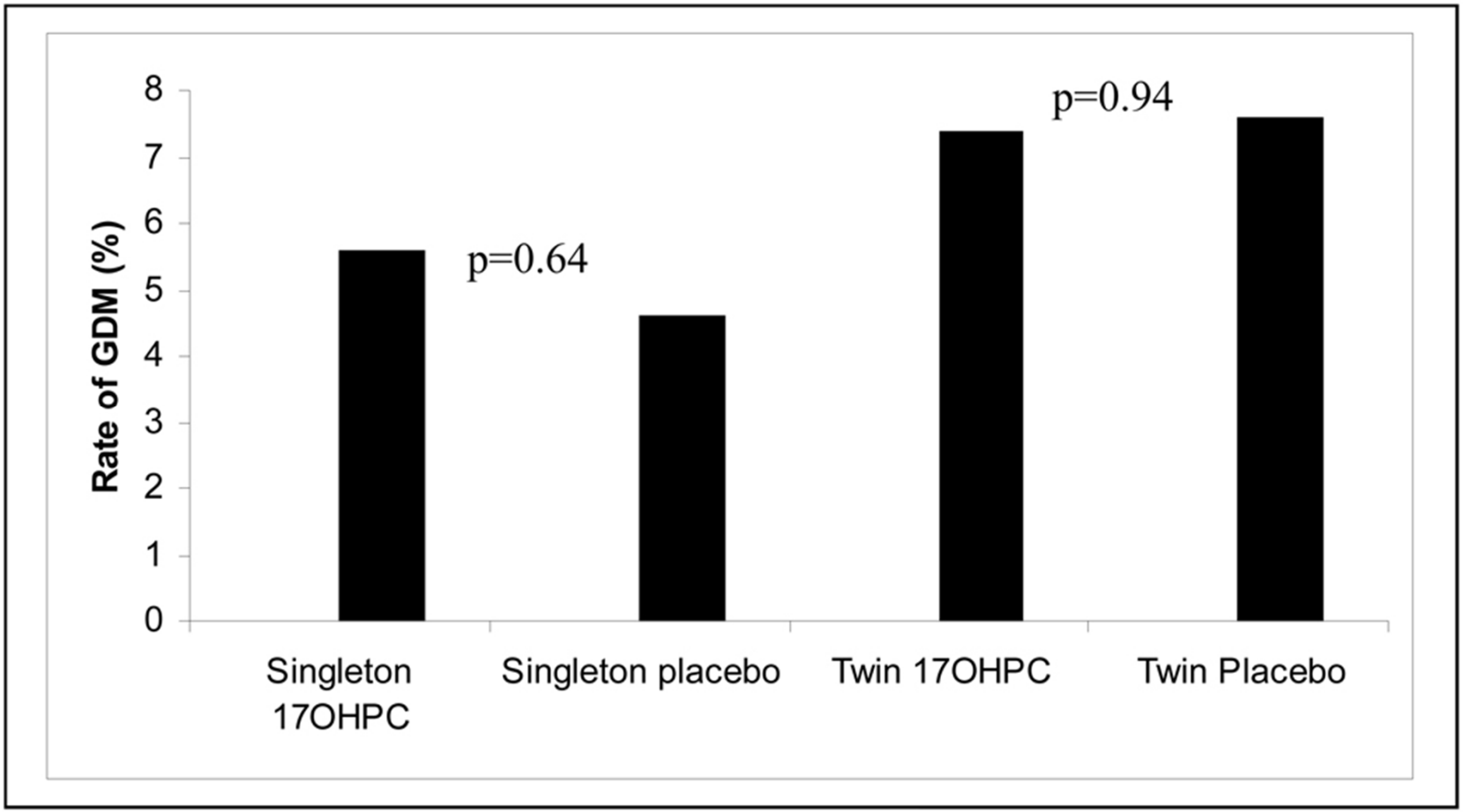
Proposed mechanisms of action reported for progestogens to prevent preterm birth[9-17]

Stimulate transcription of ZEB1 and ZEB2, which inhibit connexin 43 (gap-junction protein that helps synchronize contractile activity) and oxytocin-receptor gene
Decrease prostaglandin synthesis, infection-mediated cytokine production (antiinflammatory effects) by fetal membranes/placenta
Changes in PR-A and PR-B expression (decreased PR-A/PR-B ratio keeps uterus quiescent)
Membrane-bound PR in myometrium
PRs, when stimulated by progesterone, help selected gene promotion, or prevent binding of other factors
Interfere with cortisol-mediated regulation of placental gene expression
Nongenomic pathways
Reduce cervical stromal degradation in cervix
Alter barrier to ascending inflammation/infection in cervix
Reduce contraction frequency in myometrium
Attenuate response to hemorrhage/inflammation in decidua
Alter estrogen synthesis in fetal membranes/placenta
Alter fetal endocrine-mediated effects

PR, progesterone receptor; *ZEB1,* zinc finger E-box binding homeobox protein 1; *ZEB2,* zinc finger E-box binding homeobox protein 2.

SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.

The effect of 17-alpha hydroxyprogesterone caproate on the risk of gestational diabetes in singleton or twin pregnancies



Gyamfi C et al, Am J Obstet Gynecol 2009;201:392.e1-5.

Progesteron zur Frühgeburtsprophylaxe

Ergebnisse der Behandlung mit 17α-Hydroxyprogesteroncaproat

klinische Parameter	Studiengruppe (n = 310) %	Plazebogruppe (n = 153) %	RR einer Frühgeburt
Frühgeburt vor der 37. SSW	36,3	54,9	0,66
Frühgeburt vor der 35. SSW	20,6	30,7	0,67

Meis PJ, Klebanoff M, Thom E et al.: Prevention of recurrent pre-term delivery by 17a-hydroxyprogesterone caproate. NEngl J Med 348 (2003) 2379–2385

Frühgeburten bei Behandlung mit 100 mg Progesteron vaginal

Zeitpunkt der Geburt	Plazebo (n=70) n	%	Progesteron (n=72) n	%	Signifikanz p
<37 SSW	20	28,5	10	13,8	<0,03
<34 SSW	13	16,6	2	2,8	<0,002

Da Fonseca EB, Bittar R, Carvalho MH et al.: Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled doubleblind study. Am J Obstet Gynecol 188 (2003) 419–424

Prevention of Recurrent Preterm Delivery by 17 Alpha Hydroxyprogesterone Caproate

Paul J. Meis et al., N Engl J Med 2003;348:2379-85

Table 2. Outcomes of Pregnancy According to Treatment Assignment.*

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	no. (%)		
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54–0.81)
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)
Black women	64 (35.4)	47 (52.2)	0.68 (0.51–0.90)
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47–0.87)
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48–0.93)
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37–0.91)
Miscarriage at <20 wk of gestation	5 (1.6)	0	NA
Hospital visit for preterm labor	49 (16.0)	21 (13.8)	1.15 (0.72–1.86)
Tocolytic therapy	53 (17.3)	24 (15.9)	1.09 (0.70–1.69)
Corticosteroids for fetal lung maturity	52 (17.8)	30 (19.7)	0.91 (0.60–1.35)
Cesarean delivery	77 (25.2)	41 (26.8)	0.94 (0.68–1.30)
Chorioamnionitis	11 (3.6)	5 (3.3)	1.09 (0.39–3.09)

Table 3. Fetal and Neonatal Outcomes According to Maternal Treatment Assignment.*

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	no./total no. with data (%)		
Fetal death, antepartum or intrapartum	6/306 (2.0)	2/153 (1.3)	1.50 (0.31–7.34)
Birth weight			
<2500 g	82/301 (27.2)	62/151 (41.1)	0.66 (0.51–0.87)
<1500 g	26/301 (8.6)	21/151 (13.9)	0.62 (0.36–1.07)
Neonatal death	8/306 (2.6)	9/153 (5.9)	0.44 (0.17–1.13)
Transient tachypnea	11/305 (3.6)	11/152 (7.2)	0.50 (0.22–1.12)
Respiratory distress syndrome	29/305 (9.5)	23/152 (15.1)	0.63 (0.38–1.05)
Bronchopulmonary dysplasia	4/305 (1.3)	5/152 (3.3)	0.40 (0.11–1.46)
Ventilatory support	26/303 (8.6)	22/151 (14.6)	0.59 (0.35–1.00)
Supplemental oxygen	45/303 (14.9)	36/151 (23.8)	0.62 (0.42–0.92)
Intraventricular hemorrhage			
Grade 3 or 4	2/305 (0.7)	0/153	NA
Any grade	4/305 (1.3)	8/153 (5.2)	0.25 (0.8–0.82)
Necrotizing enterocolitis	0/305	4/152 (2.6)	NA
Patent ductus arteriosus	7/305 (2.3)	8/151 (5.3)	0.43 (0.16–1.17)
Retinopathy	5/305 (1.6)	5/152 (3.3)	0.50 (0.15–1.70)
Proven sepsis	9/305 (3.0)	4/152 (2.6)	1.12 (0.35–3.58)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2003 VOL. 348 NO. 24

"The results of our trial should be interpreted with caution. Although 17P proved to be effective in preventing preterm delivery in our cohort of women at very high risk, it may not be effective in women with a lower risk of preterm delivery, and most preterm deliveries occur in women with no previous preterm delivery. Therefore, our results may not be generalizable to women whose risk factors for preterm delivery are different from those of the women in this trial. In addition, although 17P significantly reduced the rate of preterm delivery among the women who received it, **the rate of preterm delivery in this group remained very high (36.3 percent)**. Thus, the identification of other causes of preterm delivery and other methods of preventing it remains a pressing need."

Progestational Agents to Prevent Preterm Birth: A Meta-Analysis of Randomized Controlled Trials

Luis Sanchez-Ramos et al., Obstet Gynecol 2005;105:273–9.

Table 2. Pooled Estimates of Premature Delivery According to Treatment Assignment

Study	Treatment Group	Comparison/Control	Odds Ratio (95% CI)
17α-hydroxyprogesterone			
Papiernik	2/50 (4.0)	9/49 (18.4)	0.18 (0.04–0.91)
Hartikainen-Sorri et al[26]	15/39 (38.5)	9/38 (23.7)	2.01 (0.75–5.41)
Yemini et al[25]	5/39 (12.8)	14/40 (35.0)	0.27 (0.09–0.85)
LeVine[29]	2/15 (13.3)	3/15 (20.0)	0.61 (0.09–4.34)
Johnson et al[24]	2/18 (11.1)	12/25 (48.0)	0.13 (0.03–0.72)
Meis et al[7]	11/306 (36.3)	84/153 (54.9)	0.47 (0.31–0.69)
Subtotal	137/467 (29.3)	131/320 (40.9)	
Fixed-effects model			0.48 (0.35–0.66)
Random-effects model			0.45 (0.22–0.93)
NNT	8 (5–19)		
Other progestational agents			
da Fonseca et al[8]	10/72 (13.9)	20/70 (28.6)	0.40 (0.17–0.94)
Goldzieher[27]	0/23	0/31	Excluded
Total	147/562 (26.2)	151/421 (35.9)	
Fixed-effects model			0.47 (0.35–0.63)
Random-effects model			0.45 (0.25–0.80)
NNT	10 (6–24)		

CI, confidence interval; NNT, number needed to treat (95% CI).
Data are presented as n (%).

CONCLUSION: The use of progestational agents and 17-hydroxyprogesterone caproate reduced the incidence of preterm birth and low birth weight newborns.

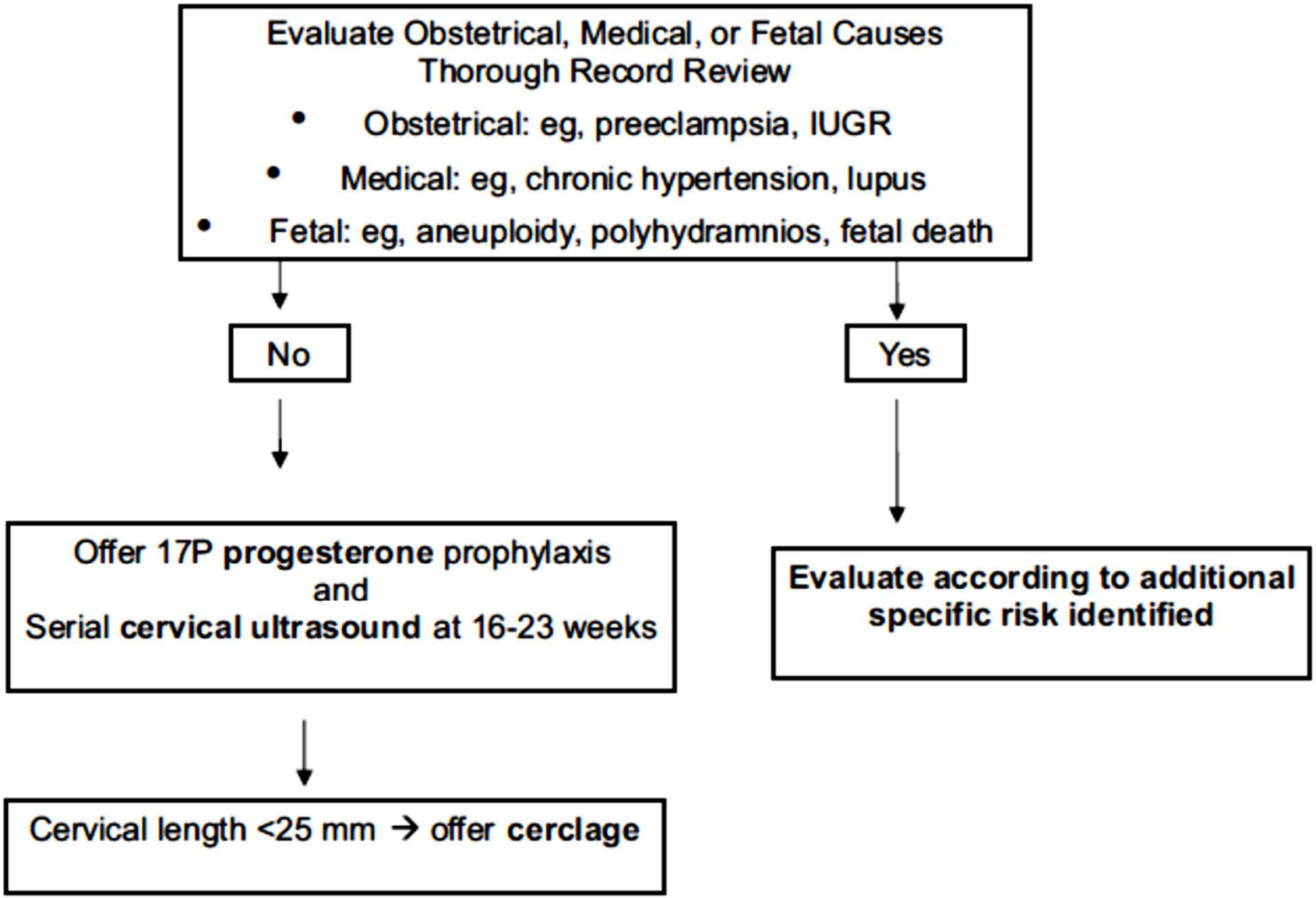
Estimated Effect of 17 Alpha-Hydroxyprogesterone Caproate on Preterm Birth in the United States

Joann R. Petrini et al., Obstet Gynecol 2005;105:267–72

- Tatsächliche Frühgeburtenrate in den USA 2002: 12,1%
- Geschätzte Frühgeburtenrate nach flächendeckender Anwendung von 17P bei Schwangeren mit Einlingsschwangerschaft und vorangegangener Frühgeburt: 11,8%
- Absoluter Unterschied: minus 0,3%
- Prozentuelle Reduktion der gesamten Frühgeburtenrate: 2%
- Anzahl der verhinderten Frühgeburten pro Jahr: ca. 9870

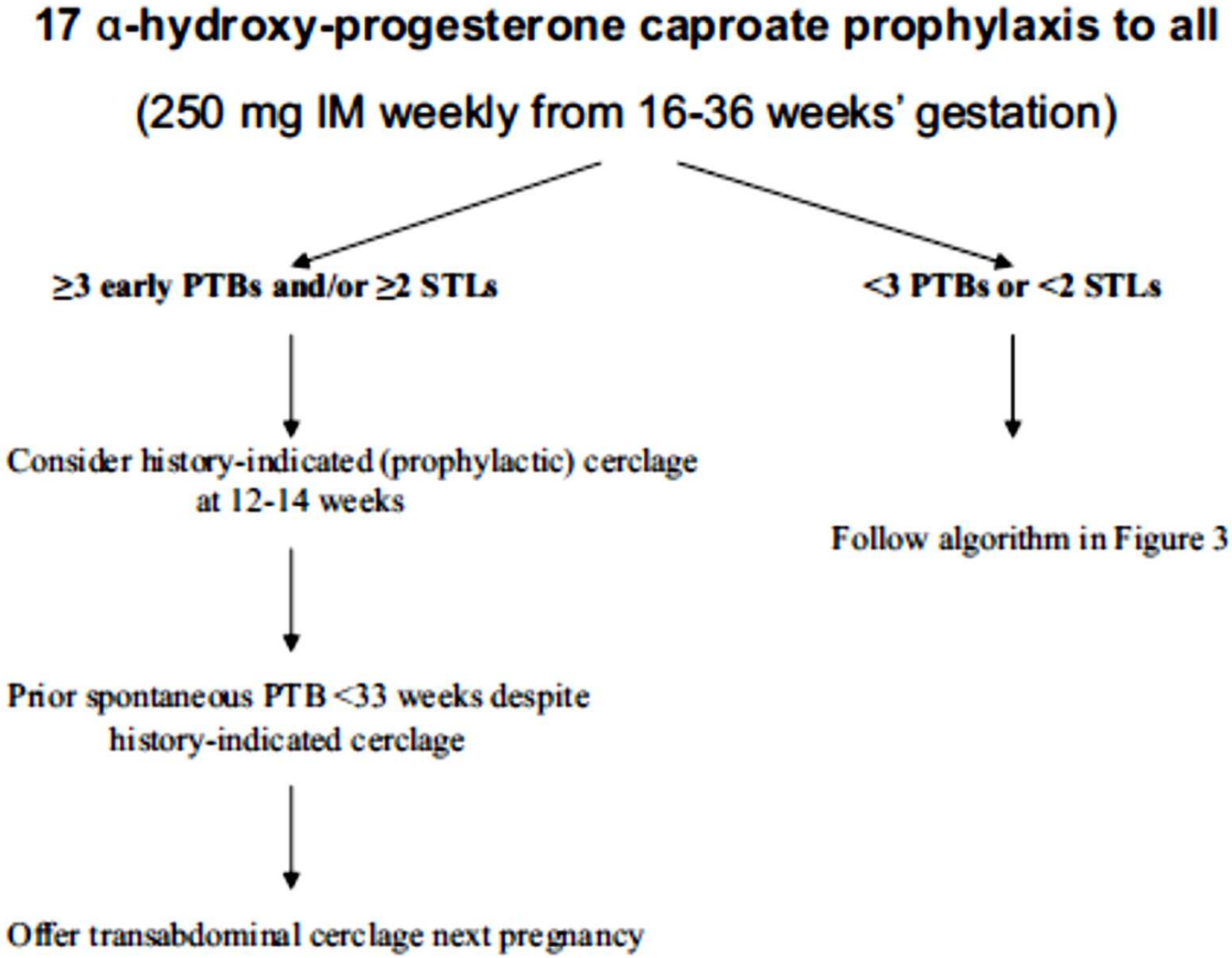
Care Algorithm for Women with a History of Birth at 16 to 34 Weeks

Jay D. Iams et al., Care for women with prior preterm birth. Am J Obstet Gynecol 2010



Care algorithm for asymptomatic women with **multiple** prior PTBs or STLs

Jay D. Iams et al. Care for women with prior preterm birth. Am J Obstet Gynecol 2010.



Progesteron bei verkürzter Zervix (ohne vorangegangene Frühgeburt)

Hassan SS et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011; 38: 18–31

- Asymptomatische Einlingsschwangere ohne vorangegangene Frühgeburt oder Spätabort
- CK-Längenmessung zwischen 19+0 und 23+6 zeigt verkürzte Zervix von 10-20 mm
- Vaginales Progesteron ab Messung bis 36+6

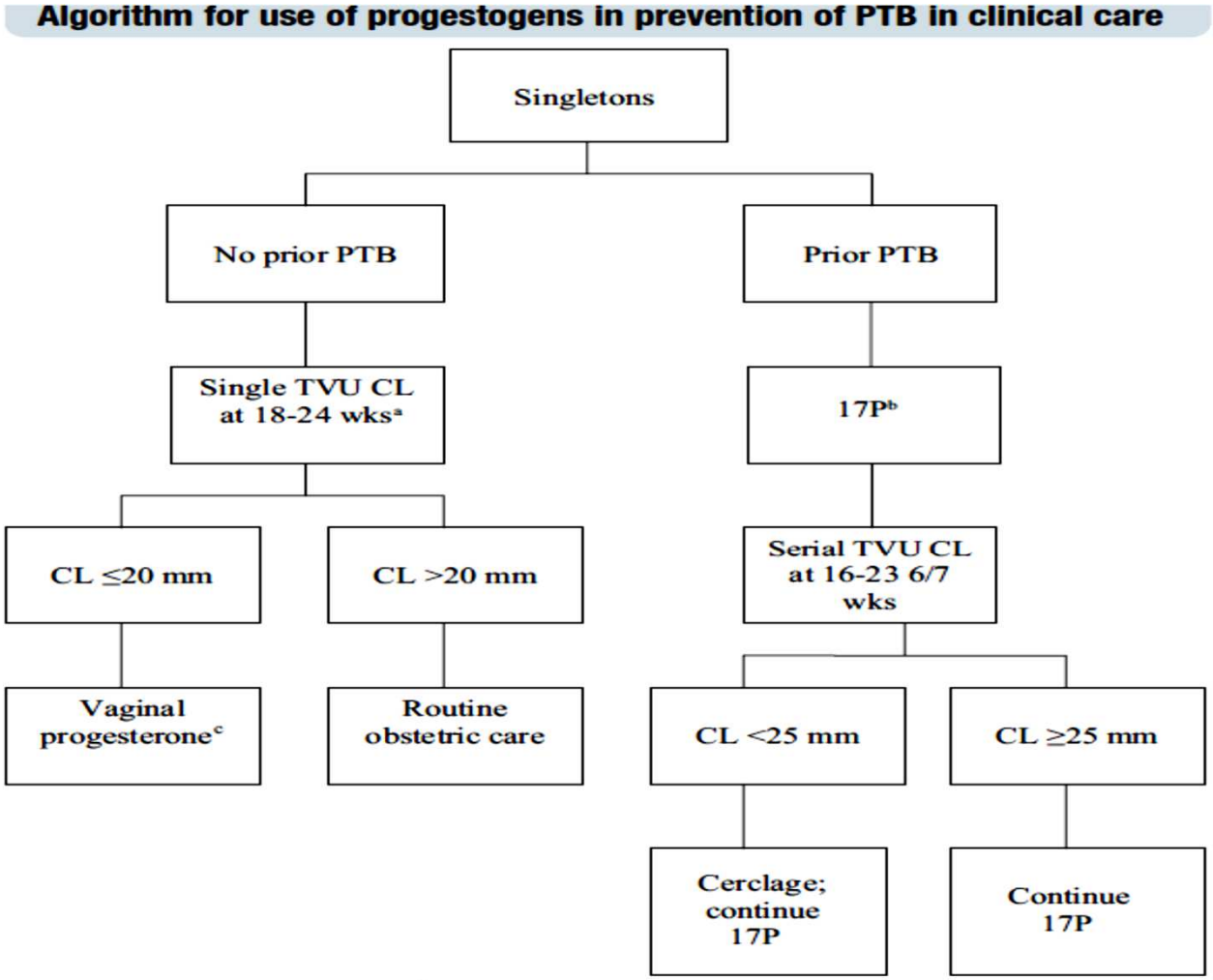
Table 2 Gestational age at delivery and neonatal outcome in asymptomatic women with a singleton pregnancy and sonographic short cervix allocated to receive vaginal progesterone gel ($n = 235$) compared with those allocated to receive placebo ($n = 223$): intent to treat analysis set

Outcome	*Vaginal progesterone* (n *(%)*)	*Placebo* (n *(%)*)	*Relative risk (95% CI)*	P
Primary outcome				
Preterm birth < 33 weeks	21/235 (8.9)	36/223 (16.1)	0.55 (0.33–0.92)	0.020
Secondary outcomes				
Preterm birth < 28 weeks	12/235 (5.1)	23/223 (10.3)	0.50 (0.25–0.97)	0.036
Preterm birth < 35 weeks	34/235 (14.5)	52/223 (23.3)	0.62 (0.42–0.92)	0.016
Preterm birth < 37 weeks	71/235 (30.2)	76/223 (34.1)	0.89 (0.68–1.16)	0.376
Respiratory distress syndrome	7/235 (3.0)	17/223 (7.6)	0.39 (0.17–0.92)	0.026
Bronchopulmonary dysplasia	4/235 (1.7)	5/223 (2.2)	0.76 (0.21–2.79)	0.678
Proven sepsis	7/235 (3.0)	6/223 (2.7)	1.11 (0.38–3.24)	0.853
Necrotizing enterocolitis	5/235 (2.1)	4/223 (1.8)	1.19 (0.32–4.36)	0.797
Intraventricular hemorrhage, Grade III/IV	0/235 (0.0)	1/223 (0.5)	0.32 (0.01–7.73)*	0.305
Periventricular leukomalacia	0/235 (0.0)	0/223 (0.0)	Not estimable	NA
Perinatal death	8/235 (3.4)	11/223 (4.9)	0.69 (0.28–1.68)	0.413
Fetal death	5/235 (2.1)	6/223 (2.7)	0.79 (0.25–2.57)	0.700
Neonatal death	3/235 (1.3)	5/223 (2.2)	0.57 (0.14–2.35)	0.431
Composite outcome scores				
Any morbidity/mortality event	18/235 (7.7)	30/223 (13.5)	0.57 (0.33–0.99)	0.043
0–4 without NICU†				0.048
0–4 with NICU†				0.068
0–6 without NICU†				0.048
Birth weight < 2500 g	60/234 (25.6)	68/220 (30.9)	0.83 (0.62–1.11)	0.213
Birth weight < 1500 g	15/234 (6.4)	30/220 (13.6)	0.47 (0.26–0.85)	0.010

Unadjusted relative risk (RR) and 95% CI calculated using the Cochran–Mantel–Haenszel (CMH) test. *Based on Logit estimator with continuity correction. †Frequency of perinatal mortality/neonatal morbidity composite scores are provided in Appendix S4 online. NA, not applicable; NICU, neonatal intensive care unit.

Progesterone and preterm birth prevention: translating clinical trials data into clinical practice, SMFM Clinical Guideline

Society for Maternal-Fetal Medicine Publications Committee, with the assistance of Vincenzo Berghella, Am J Obstet Gynecol MAY 2012, 376-86



[a]If TVU CL screening is performed; [b]17P 250 mg intramuscularly every week from 16-20 weeks to 36 weeks; [c]eg, daily 200-mg suppository or 90-mg gel from time of diagnosis of short CL to 36 weeks.

CL, cervical length; *PTB*, preterm birth; *17P*, 17-alpha-hydroxy-progesterone caproate; *TVU*, transvaginal ultrasound.

SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.

Kein Nutzen von Progesteron bei Mehrlingsschwangerschaften

- Jane E Norman et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. The Lancet, Volume 373, Issue 9680, 13–19 June 2009, Pages 2034-2040: 90 mg als vaginales Gel ohne Einfluss auf die Frühgeburtenrate

- Serra V et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. BJOG, 2013 Jan;120(1):50-7: 200 mg oder 400 mg vaginal ohne Einfluss auf die Frühgeburtenrate

- Lim AC et al. 17α-hydroxypregesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlles trial. Obstet Gynecol, 2011 Sep; 118(3):513-20: kein Einfluss auf die Frühgeburtlichkeit oder die neonatale Morbidität

TABLE 3

Current Society for Maternal-Fetal Medicine recommendations regarding use of progestogens for prevention of preterm birth

Population	Recommendation regarding use of progestogens
Asymptomatic	
Singletons without prior SPTB and unknown or normal TVU CL	No evidence of effectiveness
Singletons with prior SPTB	17P 250 mg IM weekly from 16-20 wk until 36 wk
Singletons without prior SPTB but CL ≤20 mm at ≤24 wk	Vaginal progesterone 90-mg gel or 200-mg suppository daily from diagnosis of short CL until 36 wk
Multiple gestations	No evidence of effectiveness
Symptomatic	
PTL	No evidence of effectiveness
PPROM	No evidence of effectiveness

17P, 17-alpha-hydroxy-progesterone caproate; *CL*, cervical length; *IM*, intramuscularly; *PPROM*, preterm premature rupture of membranes; *PTL*, preterm labor; *SPTB*, spontaneous preterm birth; *TVU*, transvaginal ultrasound.

SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.

Opptimum

Progesterone prophylaxis to prevent pre-term labour

Does progesterone prophylaxis to prevent preterm labour improve outcome?

What is / are the principal research question(s) to be addressed?

In women at high risk of preterm labour, does prophylactic vaginal natural progesterone, 200mg daily from 22 – 34 weeks gestation, compared to placebo:

1. Improve obstetric outcome by lengthening pregnancy and thus reducing the incidence of preterm delivery (before 34 weeks gestation)?
2. Improve neonatal outcome by reducing a composite of death and major morbidity?
3. Lead to improved childhood cognitive and neurosensory outcomes at two years?
4. Represent cost effective management for women at high risk of preterm delivery?

(Parturition Research Network, trial led by Professors Thornton and Bennett, UK)